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Mechanistic Studies and Optimization of Microwave-Assisted Palladium-Catalyzed Carbon-Carbon Bond Forming Reactions and an Academic Prospective on "Quality by Design"

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Undergraduate Honors Thesis
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Abstract

This compilation of work includes four aspects: (1) an academic review on the significance and implementation of Quality by Design (QbD), (2) mechanistic studies on the palladium-catalyzed synthesis of diarylmethanes, (3) the optimization of microwave-assisted click reactions and Suzuki couplings for use in an undergraduate organic chemistry laboratory manual, and (4) monitoring the progress of organic transformations using Raman spectroscopy.

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First and foremost, I would like to thank Dr. Nicholas Leadbeater. He has had a lasting effect on me and my undergraduate career. He has invested great time and patience in guiding and helping me do this research and construct this thesis. I would like to thank Dr. Leadbeater's whole research team for their support as well.

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All work using the microwave and Raman (interface) instrumentation and analyses of the Bobbitt oxidation reaction results, presented in Chapter 4, was done under the supervision of Kehley Davies, another graduate student working in Dr. Leadbeater's lab at the time.

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Chapter 1

The Central Role of Chemistry in "Quality by Design" Approaches to Drug Development

(To be submitted for publication in *Future Medicinal Chemistry*)

Summary

The quality of medicines reaching the consumer is strictly controlled and maintained by the regulatory agencies of the world. Pharmaceutical companies have to meet and maintain these regulatory quality standards. For this purpose, an increasing number of processes are incorporating Quality by Design (QbD) principles. Implementation of QbD involves chemistry in several ways, for example developing new synthetic and analytical methods, avoiding formation of genotoxic impurities, designing drug-like compounds to improve the quality of biological profile of medicines etc. A combined effort from regulatory authorities, pharmaceutical industries and academic research groups could also facilitate QbD implementation.

Introduction

The most important objective of the pharmaceutical industry is to provide quality medicines to the consumer. Regulatory agencies of the world, including the US Food and Drug Administration (USFDA), EU European Medicines Agency (EMA), UK Medicines and Healthcare products Regulatory Agency (MHRA**),** Japanese Pharmaceuticals and Medical Devices Agency (PMDA) control the approval and quality of the medicines reaching the consumer via various mechanisms. Under the umbrella of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the USFDA,

EMEA and PMDA together regulate pharmaceutical product registration. ICH defines the quality of a pharmaceutical product (a medicine) as “The suitability of either a drug substance or drug product for its intended use. This term includes attributes such as its identity, strength, and purity” [201]. This quality is measured and controlled by specifications that ICH has developed and define as “Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.” Clearly determining the quality standards and specifications for each individual medicine is important, and it becomes even more so when the medicine becomes generic. Pharmaceutical companies have to make continuous efforts to meet and then maintain the regulatory quality standards. Traditionally, the required quality of the medicines has been achieved and assured via testing the final product (Quality by Testing, QbT). However, more recently the concept of Quality by Design (QbD) is gaining popularity [1]. The QbD concept was first outlined by quality expert Joseph Juran [2] and now is applied to the development of most new medicines.

QbD is an important step towards the goal of providing the consumer with medicines of utmost quality. Compared with the traditional approach for drug development, which is a “react to the problem” approach, QbD is a proactive approach, where problems and risks are anticipated and measures to mitigate them are front loaded. QbD guidelines suggest a holistic approach to pharmaceutical development, where each step of the process is studied scientifically to understand how each variable impacts the quality of the product, proactive risk assessment is carried out, and the results are incorporated in designing/improving the process in an iterative fashion. The result is a dynamic process that delivers the quality and is capable of continuous improvement. The goal of QbD approach is, in Janet Woodcock’s words (Director, Center for

Drug Evaluation and Research (CDER) at FDA), “A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight”[202].There are several ways that academic groups can support the implementation of QbD in the pharmaceutical industry. In this review, we will describe four of these, namely:

1) Strengthening analytical techniques – developing highly sensitive, robust, rugged and reproducible analytical methods
2) Developing synthetic methods – cleaner reactions through the implementation of green chemistry
3) Avoiding genotoxic impurities – minimized through developing synthetic methods and purification techniques.
4) Improving the biological profile of new medicines – “designing-in” drug-like properties into new compounds.

1) Strengthening analytical techniques- highly sensitive, robust, rugged and reproducible analytical methods:

To ensure the quality of the drug substance, robust analytical methods with high sensitivity and reproducibility are essential. These methods support development of new drugs by enabling thorough study and optimization of every step of the manufacturing process. They are also key for the quality assurance and quality maintenance of the final deliverable that reaches the consumer. The principles of QbD can be applied to develop analytical tests, methods, and process analytical technology (PAT) that are robust and rugged, and will pass the definitions of the ICH and United States Pharmacopeia (USP). Broadly, there are four QbD components that can be brought to bear in the development of analytical methods (Figure 1). These can be applied in an iterative manner to continuously improve the quality of the resulting method [203].

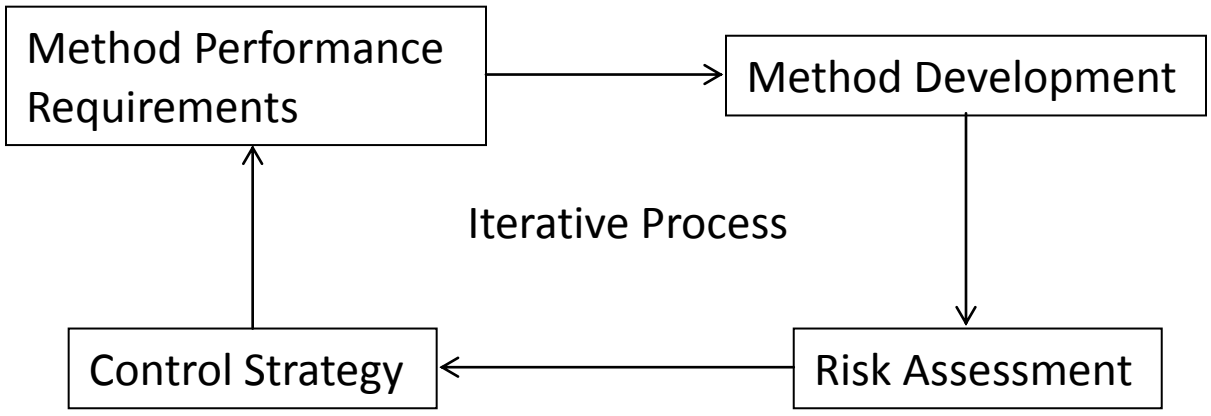


Figure 1: Application of QbD to Analytical Method Development

i. Method performance requirements: Initially it is essential to define clearly and understand the objective of the analytical method. The target performance criteria are

defined by the critical quality attributes (CQAs) and specification limits, including precision, selectivity and sensitivity of the analytical method. Another performance component is the operational intent, which includes aspects that facilitate the routine use of the method, e.g., the equipment, solvents etc.

ii. Method development: Once the method requirement is established, the next phase is method development. It is the most important phase. For a rugged and reproducible method, QbD guidelines suggest that the method should be designed to meet the objective, based on the best scientific knowledge and expertise, using common techniques as much as possible to avoid unnecessary diversity and making appropriate selections to address/avoid any potential issues.

iii. Risk Assessment: Analytical method needs to be rugged enough so that they can be reproduced identically when they change hands or equipment. This can be achieved by thinking proactively about possible risks that might impact the performance criteria. Several tools have been developed that could be helpful in systematically carrying out the risk assessment process. One example is represented in Figure 2 [3]. All the steps in the analytical method (sample preparation, chromatography, data analysis) are considered separately, and a cause-and-effect diagram, also known as a fishbone or Ishikawa diagram, is developed. This is more effective in identifying all the factors that might impact the method performance and developing strategies to control them. Other risk assessment tools are priority matrices, failure mode effect analysis (FMEA)[204], and CNX (controlled [C], potential noise factors [N], experimented

[X])[203]. A robust and well thought-through risk assessment can be performed by using these tools in combination [4,5].

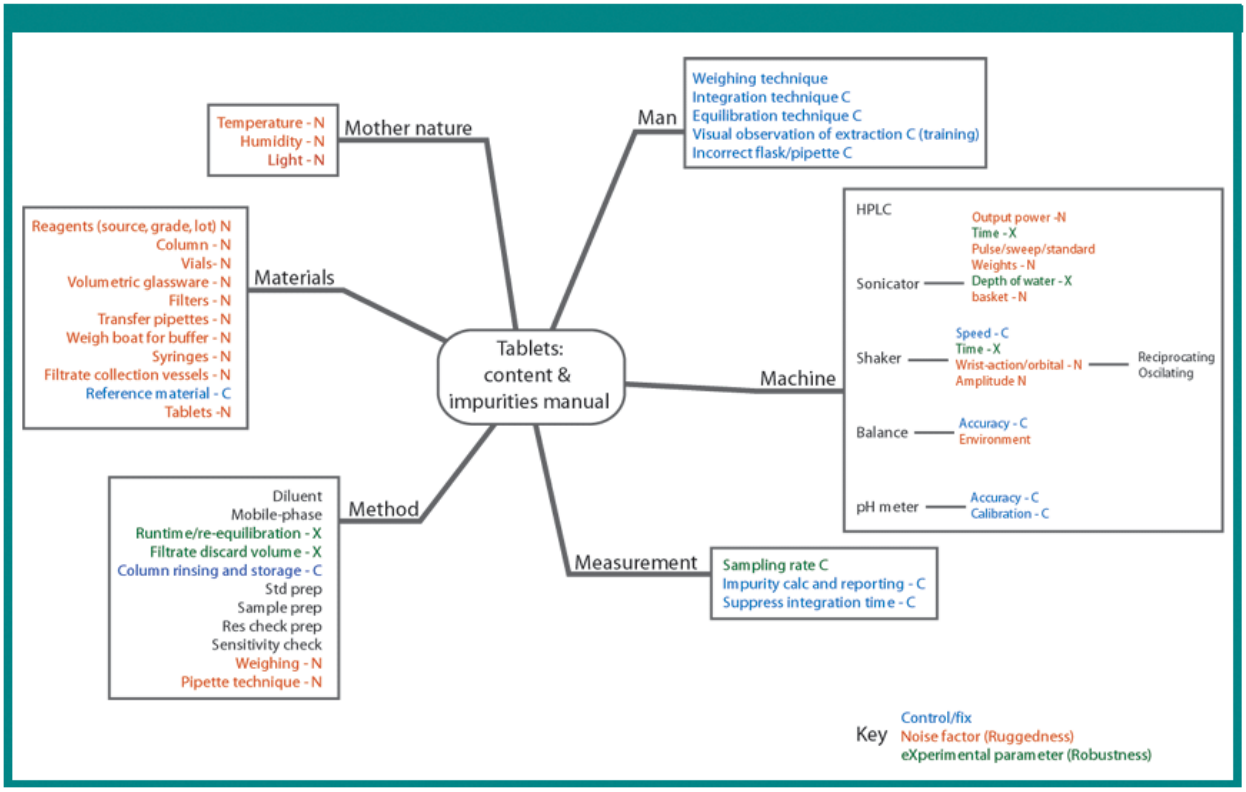


Figure 2: Fishbone diagram created for an HPLC assay and impurities method (reproduced with permission from reference 203)

iv. Control Strategy: Once the method is developed and its risk assessment is completed, it is important that the robustness and reproducibility is maintained throughout its life. This is achieved by developing a strategy to control all the attributes of the method, by defining the allowed limits of any changes in the method environment that can affect its

operation. Any changes in the method for improvements are also allowed with reference to the control strategy.

Adhering to QbD guidelines will lead to robust and sustainable analytical methods and a higher transfer success rate than with traditional technology-transfer approaches. It will ensure that the products reaching the consumer are of high quality, possessing reliable potency and safety.

Looking to the future, it will be important to develop global approaches and guidelines for analytical methods. Application of QbD to method development will facilitate this. A common criteria and language is important, so that new tools and skills can be developed more effectively. Currently it seems that these approaches and technologies are being developed in isolation and separately for each product. Another hurdle that holds progress back is that the new state-of-the-art technologies are not always applied in method development. For example, supercritical fluid chromatography (SFC), which has become very popular in the discovery phase, is quite rarely used by researchers in the development stage in the pharmaceutical industry.A common, high level initiative is needed, where a consortium of international pharmaceutical companies and regulatory authorities facilitate development of core technologies that could be applied commonly for various purposes. Scientific groups in industry and academia would then be enabled to work together to develop analytical methods that would ensure high-quality medicines reaching the consumer.

2. Development of Synthetic Methods – cleaner, greener reactions:

Quality of a pharmaceutical product can be improved by devising processes that give cleaner products, reduce or eliminate toxic side-products and minimize the environmental impact. In the last 150 years, chemistry has transformed the modern life by providing access to essential chemical entities; perfumes, plastics and pharmaceuticals etc. Numerous synthetic protocols have been developed to manufacture these compounds. A large majority of these conventional synthetic methods are founded on petroleum-based feedstock and solvents. High consumption of petroleum based chemicals is becoming an unsustainable burden on the earth's natural resources. Also, conventional synthetic processes often produce side-products, which can be toxic and end up in the end-of-the-pipeline products or are released into the environment. The pharmaceutical industry is clearly under a lot of pressure to produce their drugs free of toxic side-products and in an environmentally benign fashion. Under the general area of "Green Chemistry" the chemistry community is redesigning synthetic processes. This requiresthe use of greener solvents and reagents, proper choice of starting materials, improving atom economy, minimizing the number of steps and developing efficient purification and isolation methods. To measure how green is a chemical process, a standard set of 12 principles has been developed [6,7]. It is summarized below in the memorable acronym "PRODUCTIVELY" [8]:

Prevents wastes: The waste is prevented, minimizing the need to treat or cleanup waste.

Renewable materials: The feedstock or the raw material is renewable, to minimize the depletion of natural resources.

Omit derivatization steps: Use of protecting groups is minimal or completely avoided, because it reduces atom economy and increases waste.

Degradable chemical products: Chemical products degrade after their function is complete and do not persist in the environment.

Use safe synthetic methods: Synthetic methods are designed to eliminate use and production of substances that pose toxicity to human health and environment.

Catalytic reagents: Use of catalysts is maximized, and stoichiometric reagents are minimally used.

Temperature, pressure ambient: For safer chemistry and accident prevention.

In-process monitoring: Applying analytical methods that allow in-process, real time monitoring and control of formation of hazardous materials.

Very few auxiliary substances: Use of auxiliary substances, like solvents, separation reagents etc., is minimal.

E-factor (environmental factor) maximize feed in product: Maximize atom economy, by designing synthetic methods that maximize the incorporation of all materials used in the process into the final product. E-factor is the mass of waste generated in a process divided by the mass of product.

Low toxicity of chemical products: Chemical products maintain their functional efficacy and have minimal or no toxicity

Yes, it is safe: The process is designed to be safe, avoid accidents, and avoid production of toxic chemicals.

The “E-factor”(environmental factor) is a particular important parameter for measuring how green a manufacturing process is in terms of the impact it makes on the environment [9]. It is the mass of waste generated in a process divided by the mass of product. A lower E-factor means a greener process. It is a commonly perceived that large scale processes for bulk chemicals would have high E-factors. However, in reality pharmaceutical chemistry processes have a much higher E-factors (>100) compared to the bulk chemical industry (E-factor typically <5). For example, the original synthesis of ethylene oxide involved a cyanohydrin intermediate. Its E-factor was 5. The modified synthesis uses molecular oxygen and has an E-factor of 0.3. It also does not use chlorine (Figure 3) [10].

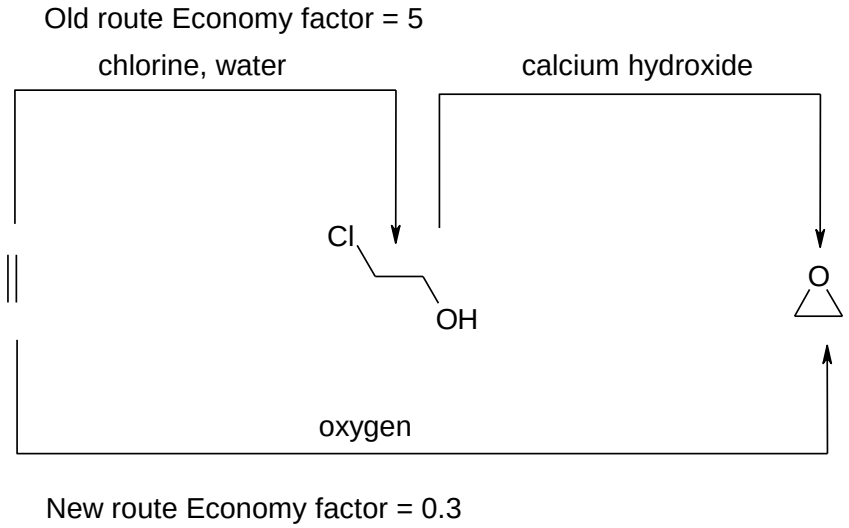


Figure 3: Manufacturing process of ethylene oxide

Another way to improve the E-factor of a reaction is to increase atom efficiency. This can be achieved by employing catalysts for reactions that had previously required stoichiometric reagents. One example where use of catalysts has made a significant impact is the synthesis of ibuprofen (Figure 4) [11].The original synthesis included 6 stoichiometric steps, with a low atom

efficiency of 40%. The modified synthesis, takes the catalyst-innovation to the max, and includes 3 catalytic steps instead. Hydrofluoric acid, in the acylation step, serves both as the catalyst and the solvent. Both HF and acetic acid generated in this step are recovered and recycled, making this synthesis virtually 100% atom efficient. This innovative technology received the Kirkpatrick Achievement Award for "outstanding advances in chemical engineering technology" in 1993 [206].

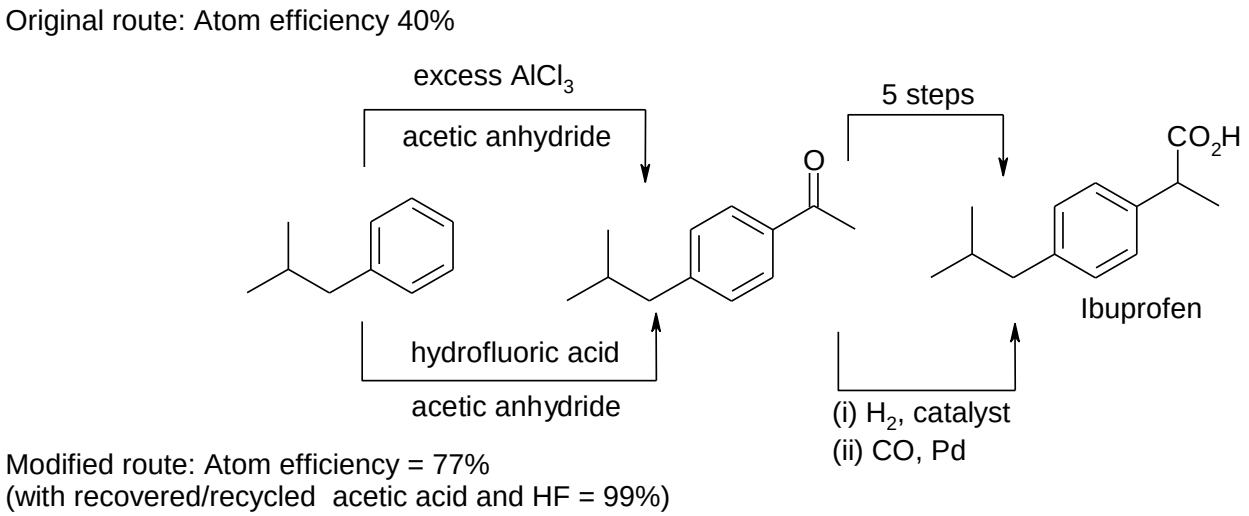


Figure 4: Synthesis of ibuprofen

Solvents, used in a process to carry out reactions and isolation and purification of the products, are often the major contributors to waste generated. Developing methods aimed at solvent reduction has a significant impact on the E-factor of an overall process. For example, the method for manufacturing sertraline (an antidepressant) used to consume 250,000 liters of solvent for each 1,000 kg of product. Modifications have reduced the use of solvent by 10-fold (Figure 5) [12]. One of the important changes in the new synthesis was that the last three steps were carried out in ethanol. This meant that these steps could be carried out in a single pot, and also eliminated the use of toxic solvents such as tetrahydrofuran, toluene and hexane.

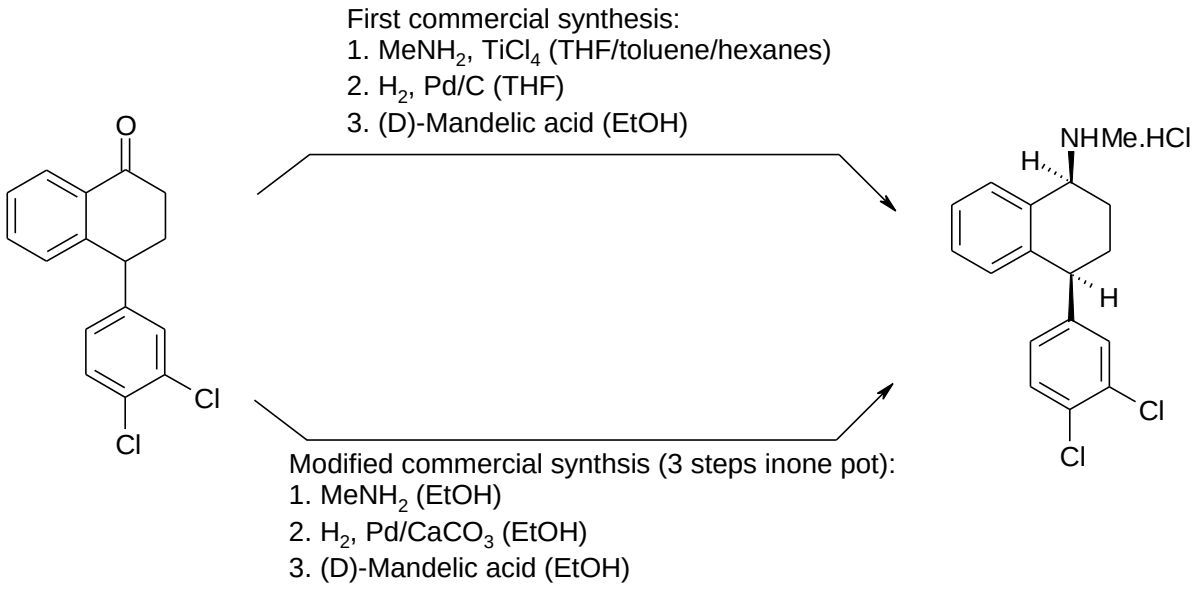


***Figure 5**:* Improved synthesis of sertraline

Many conventional solvents are flammable and/or toxic. They are usually volatile and pollute the atmosphere. Discovery of alternative solvents that are not flammable, toxic and volatile is a main focus of green chemistry research. Examples include supercritical carbon dioxide, ionic liquids and water. Supercritical CO_2 is non-toxic and the solubility of substances varies with the pressure of CO_2 [13]. This property can be used in purification and separation methods; increase in CO_2 pressure can decrease the solubility of some compounds in water causing them to precipitate out. Supercritical CO_2 is also becoming a commonly used mobile phase in extraction and separation science [14]; decaffeinating coffee probably being the most commonly known use of supercritical CO_2. Ionic liquids are organic salts that are liquid at room temperature. They have negligible vapor pressure and thus are not lost into the atmosphere [15]. However, they can be very toxic and so should be used with care. Water is one of the more commonly used green solvents [16]. Many commonly used reactions in the pharmaceutical industry have been modified for use in water. For example, palladium-catalyzed

C-C bond forming reactions, can be performed in water as the solvent, often using very low catalyst loadings in conjunction with microwave heating (Figure 6) [17]. However, the true "greenness" of water as a solvent is sometimes overstated. Intuitively, something so ubiquitous as water and indeed so essential to life should automatically qualify it as "green," but overlooked is the fact that it cannot be incinerated after use and it takes a considerable amount of energy to distill water in order to purify it. Water purification at treatment plants is also a costly and energy-intensive endeavor. Indeed, when evaluated using a full complement of the most essential metrics, it has been reported that, "water is only a truly green solvent if it can be directly discharged to a biological effluent treatment plant." Obviously, dissolved heavy metal catalysts, ionic phase transfer reagents, trace amounts of newly-synthesized organic compounds whose human or aquatic toxicology is likely unknown would render water unfit to this type of disposal. This said, water still represents an attractive solvent and likely a greener choice than most if appropriate pre-disposal treatments are employed. [18]

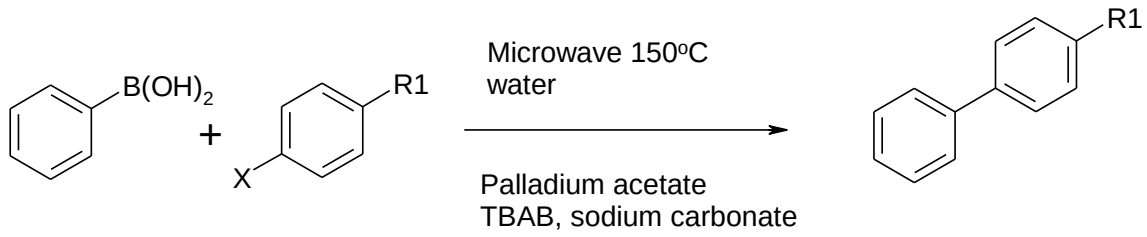


Figure 6: Suzuki coupling reaction in water as the solvent

Overall, using green chemistry principles, it is possible to produce cleaner end-of-the-pipeline products, avoid the use and production of toxic chemicals and reduce environmental burden by making reactions more efficient and less polluting. In addition, pharmaceutical companies are finding that employing greener routes to their target compounds has not only an

environmental benefit but can also be advantageous financially. For example, less waste means lower disposal costs and higher atom efficiency means more value for money from reagents.

3. Genotoxic Impurities – minimize through developing synthetic methods and purification. Genotoxins are compounds that have the capability to damage the genetic material of cells, potentially leading to tumor development [19]. DNA damage in reproductive cells (eggs and sperm) can be inherited by the offspring and can inherit certain disorders [20].Sometimes the DNA damage is additive in nature, the body "remembering" it, and effects becoming exacerbated each time a person is exposed to the genotoxin. During the synthesis of active pharmaceutical ingredients (APIs) and their formulation to make the drug product, numerous chemically reactive reagents are used, synthetic intermediates formed and side products produced, any of which could feasibly lead to contamination of the drug product with impurities that possess potential for genotoxicity (PGIs). Several molecules have been positively identified to be genotoxic over the years and, based on these, compound classes and structural moieties (called structural alerts [21]) have been flagged [22]. Examples include alkyl halides, alkyl sulfonate esters [23], and hydrazines [24]. These, and a variety of others that can raise possible concern for mutagenic activity or DNA reactivity, are outlined in Figure 7 [22]. Also, based on the DNA reactivity assessed by Ames tests on many compounds (>8000), several software systems, (e.g. DEREK, TOPKAT, MCASE) have been developed to predict potential genotoxicity [25]. Also, it is possible to track potential PGIs during the development process.

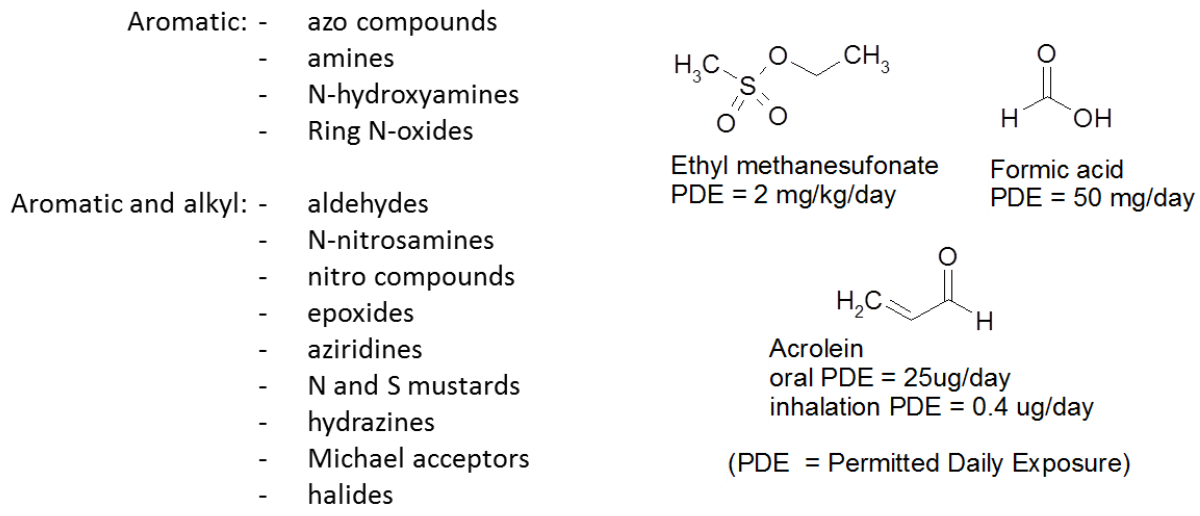


Figure 7: Examples of structural alerts for genotoxicity and a few known genotoxins

Currently, the quantity of genotoxic impurities permitted in pharmaceutical compounds is regulated by the Threshold of Toxicological Concern (TTC) [26]. TTC of an impurity is the level of that impurity, beyond which it would potentially cause harm to patient health [205] [27,28]. In an article, scientists from various major pharmaceutical industries such as GlaxoSmithKline, AstraZeneca, Pfizer, Johnson & Johnson, and Hoffman-La Roche, proposed a methodology to determine the level of exposure that would be of genotoxic concern for patients [22]. The article describes allowable daily intakes of various genotoxic impurities, which ranges between approximately 1.5 µg/day for lifetime and 120 µg/day for less than a month. The allowable level of a genotoxic impurity in a medicine can be calculated from the daily dose of the medicine and the TTC value of the impurity.

QbD approaches have been applied to eliminate or minimize the contamination of APIs with genotoxic impurities. Instead of purifying the final product by employing detection methods and separation techniques to remove genotoxic impurities (quality control or assurance), QbD

can be used to study and systematically optimize every step of the process individually to minimize undesired contaminants. A recent article by research scientists at Vertex Pharmaceuticals highlights the importance of identifying and removing PGIs from drug candidates during the development process [19].QbD tactics include analyzing the synthetic scheme to identify proactively the stages where possibilities of genotoxic impurity formation exist, analyzing the fate of these undesired contaminants (whether they will get eliminated or survive in the subsequent chemical steps), remodeling the synthetic approach to eliminate starting materials and reagents that are known to be genotoxic, optimizing each synthetic step by varying reaction conditions, and finally checking the quality of the final product. An example of a step in a reaction sequence that was studied by applying such QbD guidelines is outlined in Figure 8 [19]. It involves the reduction of a nitroaromatic compound to the corresponding anilines using a palladium-catalyzed hydrogenation. There are two potential undesired side products arising from partial hydrogenation; namely a nitroso-compound and an N-hydroxylamine [29]. Several variables of this reaction were studied independently, including the amount of catalyst used, the reaction time, temperature, pressure, and the solvent in which the reaction was performed. The amount of the two genotoxic side products was determined over a series of permutations and combinations of reaction conditions. Selected data is presented in Table 1 [19]. Based on the results, it was possible to select the best reaction conditions to yield the desired product with the concomitant formation of the least amount of the impurities. In this way, by applying QbD guidelines a process can be designed such that, ideally, the genotoxic impurities would never be generated, or their formation would be minimized. Use of the principles of green chemistry can also play an important role in this, as described in Section 2.

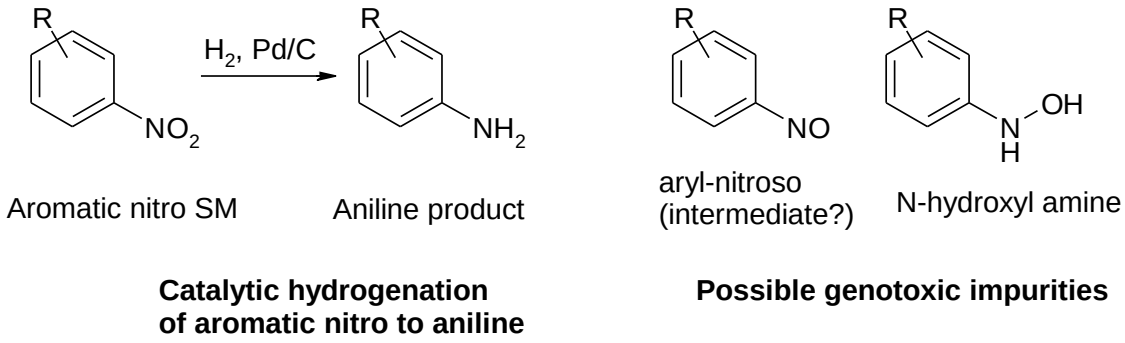


Figure 8: Catalytic Reduction of Aryl Nitro Compound to Corresponding Aniline

Pd loading (wt % wet)	Temperature (°C)	Time (h)	Compounds in product mixture (%area)[a]			
			Aniline product	Nitroaromatic SM	N-hydroxyl amine	Aryl-nitroso
2.5	15	18	72.01	17.55	9.58	0.73
2.5	25	18	99.12	0.31	0.14	0.22
5	25	18	99.74	-	-	-
7.5	15	18	99.66	-	-	-
7.5	25	8	99.71	-	-	-
2.5	15	8	50.99	42.12	5.65	1.16
2.5	25	28	99.77	-	-	-

a= (-) not detected

Table 1. Compound distribution obtained when varying reaction conditions for a palladium-catalyzed hydrogenation

4. Pharmaceutical view point: Improving the biological profile of new medicines- "designing-in" drug-like properties into new compounds

Reviews on the topic of QbD have mostly been focused on the synthesis of clinical candidates and drug compounds. Quality of the biological profile that is designed into these molecules is much less discussed. The biological profile of a drug compound is equally, if not more important, than the synthetic process that is used to make it. An ideal drug would modulate only the desired (target) biology and nothing else. Such "magic bullets" do not exist in reality and inventing drugs that have a clean profile is remarkably challenging. Over several decades, research has identified several properties that a good drug should have, and molecular or structural moieties that would incorporate these drug-like properties into the drug molecules. Despite these advancements, a large majority (>95%) of drug candidates fail during the clinical development process. Understanding which structural moieties bring about particular drug-like properties is very important. By front-loading drug-like properties, QbD can improve the chances of success in the clinical development of drug candidates [30].

In addition to potency and selectivity towards a biological target, a drug needs to have good pharmacokinetic (PK) properties. When administered, in addition to the target biology four PK processes take place; absorption (A), distribution (D), metabolism(M) and excretion(E), together known as ADME. Absorption is the process of the drug entering the blood circulation, distribution is spreading of drug into various body parts, metabolism is the process of degradation of the drug molecule into metabolites, and excretion is the elimination of the drug and its metabolites from the body. In achieving a good PK profile, an optimal balance of ADME is needed. ADME properties of a drug contribute to the profile of a drug in several ways,

including its route of administration (oral, intravenous etc.), the size and frequency of the dose, how it should be taken (e.g. on empty stomach or with food), what other drugs need to be avoided (drug-drug interactions), and others. Optimal PK improves the probability of success in the clinic. Over several decades several principles have been developed, correlating the ADME properties of compounds to their physicochemical properties, including solubility, lipophilicity, and polar surface area, and in turn, the physicochemical properties to the molecular features, including, molecular weight, number of heteroatoms, and substitution pattern [31,32,33]. Using these guidelines, medicinal chemists optimize the compounds to convert them into drugs. One of the more widely used guidelines for building in drug-like properties has been Lipinski's rule of five (RO5) [34]. It was derived from an analysis of compounds that have entered phase II clinical trial. In other words, these compounds have the optimal PK for successful development. In a recent article, Vertex researchers have studied changes in properties of compounds discovered by pharmaceutical research over time [30]. They compared criteria, such as, molecular weight, clogP, polar surface area, rotatable bonds, hydrogen bonding groups, molecular complexity, flatness, and molecular frameworks of the discovery compounds reported in the Journal of Medicinal Chemistry between 1959 and 2000 that have subsequently become marketed drugs.

The mean molecular weight of discovery compounds and drugs has increased over the years with the most dramatic increase being in the early 1990's (Figure 9). This trend has also been seen with Pfizer and Merck clinical candidates from the sixties up to 2000 [34]. Increased molecular weight in general leads to decrease in aqueous solubility and permeability resulting in poor bioavailability and thus could contribute to failure in the clinic.

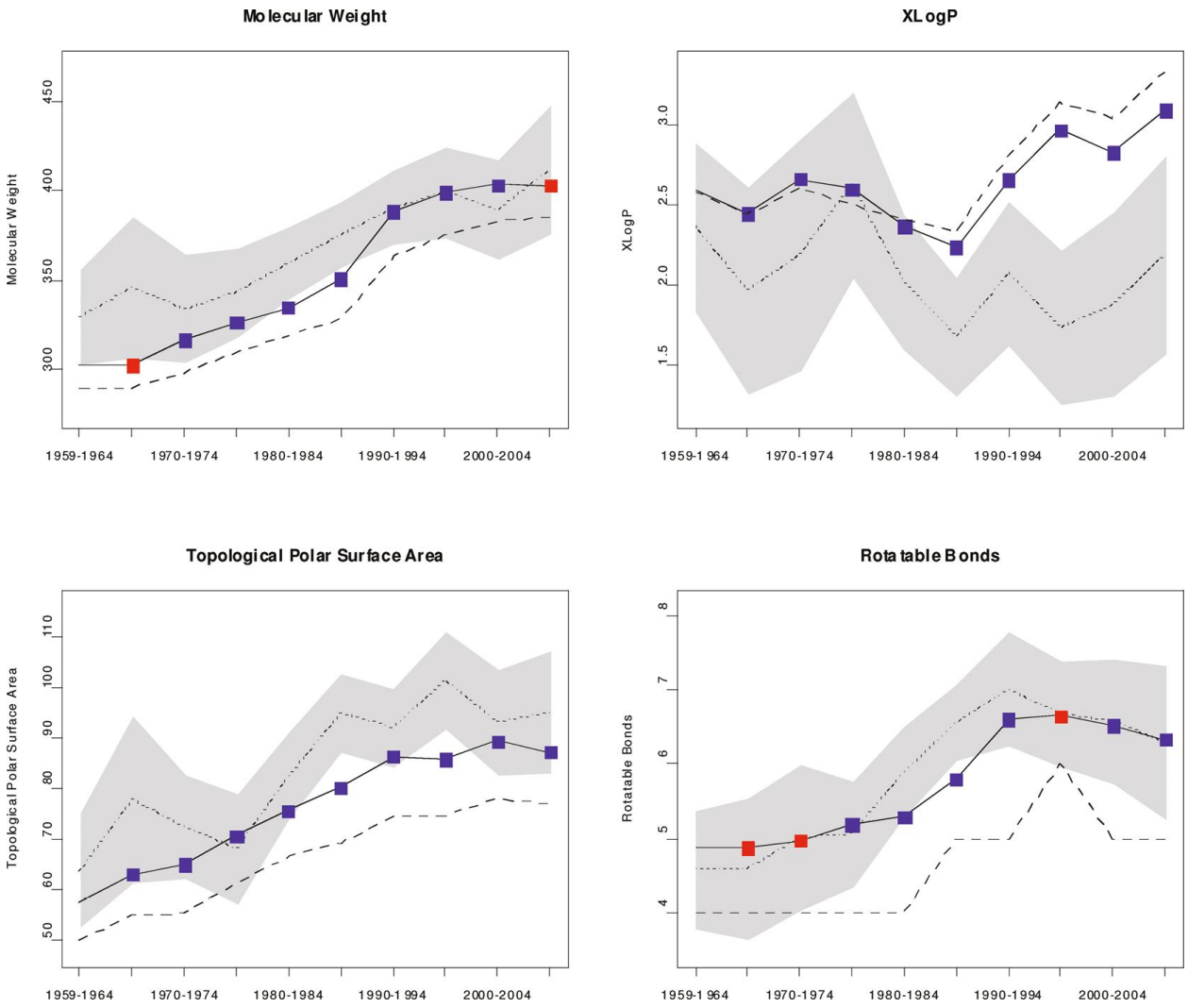


Figure 9. Mean values for molecular weight, CLogP, polar surface area, and number of rotatable bonds for molecules published in Journal of Medicinal Chemistry in 1959-2009 are shown as solid lines with squares. Blue squares indicate a statistically significant difference between the mean for a particular 5-year interval and the preceding interval. Red squares indicate that the difference was not statistically significant. Dashed lines indicate the median value for each property during the designated interval. The gray regions represent the 95% confidence interval

for drugs launched during the same time period, with the dotted line representing the mean value for drugs during each 5-year period. Reproduced with permission from reference 30.

Since the mid-1970's an increase in lipophilicity (logP) of synthesized compounds has also been observed, probably because in most cases increasing logP leads to improved potency. However, increased logP carry a baggage with it and can be correlated to decreased solubility and permeability, increased hERG binding and CNS penetration (disfavored unless it is a CNS target) and toxicity (by hitting undesired targets). In contrast, the logP of marketed drugs has decreased since the mid-70's. Several studies have shown that compounds with lower polar surface area (PSA) have good absorption increasing their probability of being orally available [35,36].But a trend of increased PSA has been observed for both discovery compounds and marketed drugs. Some reports have shown correlation between number of rotatable bonds and oral bioavailability [37,38,39]. However, a general trend of increasing rigidity is observed during the design and optimization of compounds.

Another important parameter that affects absorption and hence bioavailability of a compound is the number of atoms it has that can form hydrogen bonds [40,41]. Lipinski states that less than five hydrogen bond donors and less than hydrogen bond acceptors are optimal for drug-like properties [34]. This rule is followed in the industry and the number of hydrogen bonding groups in the compounds synthesized has been essentially held steady for the past twenty years. There is no direct measure of properties like molecular complexity and frameworks. However, a group at Novartis has used the number of structural features present in various

molecular fingerprints and descriptors as a measure of complexity and they found that that with increasing potency of the ligands, the molecule's average complexity also increases [42]. It is therefore not surprising that the complexity of discovery compounds synthesized has increased and, as a consequence, as has that of marketed drugs. To compare the molecular framework of compounds atoms in each molecule have been grouped into ring, linker, framework, and side chain atoms [43]. Analysis shows that the diversity of shapes in the set of synthesized compounds is extremely low.

The aromatic character (flatness) of compounds is also of significance as it can be related to aqueous solubility and melting point. Fractional sp^3 character (Fsp3) has been used to measure flatness of a compound. This property is important since the possibility of hERG binding, cyp inhibition increases with the number of aromatic rings [44,45]. Fsp3 of synthesized molecules increased until the mid-nineties followed by a steady decrease until 2009 and is lower than that of marketed drugs. This is probably a result of easy Pd-mediated synthetic methodologies available for sp^2-sp^2 couplings.

Another property of a compound that contributes to good ADME is metabolic stability. If a compound is metabolized rapidly, its duration of action (half-life) is short and that might result in lower efficacy and the need for more frequent dosing. Sometimes metabolism can result in toxic metabolites being formed. Primary metabolism is carried out by Cyp enzymes, and usually involves replacement of a H-atom with a hydroxyl group. Several strategies have been developed for slowing down metabolism, such as lowering lipophilicity and blocking metabolic sites, amongst others. Replacing aryl rings with heteroaromatic analogs is a commonly used

strategy for lowering lipophilicity. Substitution of metabolic hot-spots with groups like, F, Cl, CF_3, CH_3can often block metabolism [46,47]. An example is shown in (Figure 10) [48].

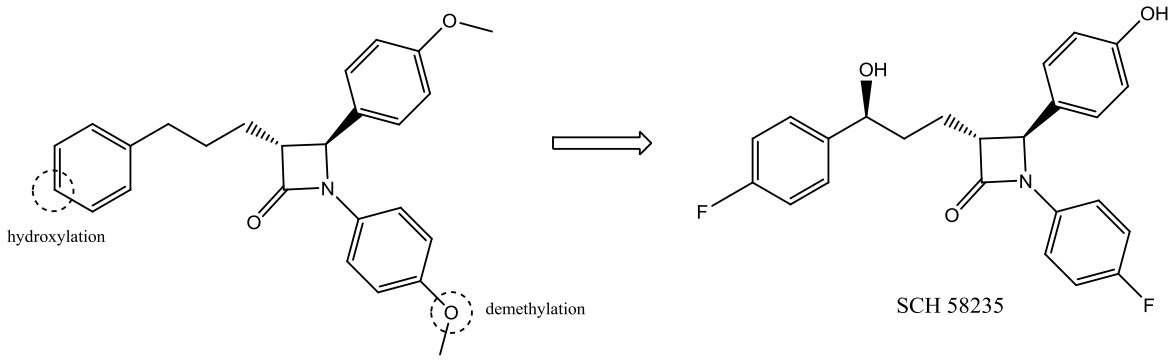


Figure 10: Design of SCH 58235, dashed circles show site of metabolism blocked by substitution with fluorine resulting in improved in-vivo potency.

Overall, the properties of compounds being synthesized and marketed drugs have changed over the years for the worse, even though several guidelines have been developed and brought forward to incorporate drug-like properties. There are several structural features that have been recognized to be drug-like; sp^3 carbons, heteroatoms, heterocycles, aliphatic rings, sulfones, and sulfonamides as well as H-atom substitutions like F, Cl, CF_3, CH_3. The majority of synthetic method development is focused on aromatic and sp^2 carbon chemistry. There are very few methods for incorporation of F or CF_3 groups into molecules but this is certainly an area of significant current research interest [49].Often, structural diversity of synthesized compounds is limited by the availability of starting materials. More emphasis needs to be put on synthetic chemistry in this direction.

Conclusion

The quality and efficacy of medicines can be improved, controlled and maintained by implementing the tenets of QbD. Failure rates could be decreased and thus development costs also reduced. The dynamic nature of QbD allows for adjusting to the new risks throughout the life of a medicine, implementation of new technology, and hence continuous improvement in the quality of the product. A tremendous advancement has been made in this field, but there is still a lot of room for further improvement and a many opportunities exist and new ones are emerging. Biological quality can be designed in early on by using the medicinal chemistry knowledge base. Thinking from a QbD mindset, the need for new technologies should be anticipated, including general analytical methods and new chemical reactions that are greener. These developments may facilitate the drug discovery process as well as avoid formation of genotoxic impurities in the synthetic chemistry sequence. At present, QbD efforts are being made in a rather isolated and discrete manner. A more global and holistic approach should be taken, where the regulatory agencies, pharmaceutical companies and academic institution work together, to develop common strategies and practices that are applicable to a variety of QbD objectives.

Financial Disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials

discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

Key Terms:

Supercritical Fluid Chromatography (SFC) is a technique used to purify compounds with low molecular weight and chiral molecules. It uses carbon dioxide as the mobile phase and therefore the chromatographic flow path must be pressurized.

Supercritical carbon dioxide is a liquid state of carbon dioxide. Supercritical CO_2 is an important commercial and industrial solvent because of low toxicity and environmental impact. Also its low temperature allows purification of thermally unstable molecules.

Atom Efficiency is calculated by dividing the molecular weight of the product by the sum total of the molecular weights of all substances produced in the stoichiometric equation for the reaction(s) involved. It is used to measure the amount of waste generated.

Fishbone Diagrams are cause and effect diagrams which demonstrate the many potential causes for a problem or effect.

Active Pharmaceutical Ingredients A drug consists of two ingredients, one is the active drug (API) and the other is the excipient which is inactive and acts as a carrier of the drug

Executive Summary:

Quality by Design

- Pharmaceutical companies make continuous efforts to meet and then maintain the regulatory quality standards. Recently the concept of Quality by Design (QbD) is gaining popularity and is replacing the traditional Quality by Testing (QbT) approach. There are several ways implementation of QbD can be facilitated.

Strengthening analytical techniques- highly sensitive, robust, rugged and reproducible analytical methods

- The principles of QbD can be applied to develop analytical tests, methods, and process analytical technology that are robust and rugged
- Four QbD components can be applied to developing analytical methods. These can be applied in an iterative manner to continuously improve the quality of the resulting method

Development of Synthetic Methods - Cleaner reactions

- Green chemistry: Traditional synthetic processes often use toxic starting materials, reagents and solvents. Developing chemical processes that are green could minimize the use and production of these toxins and thus help improve quality of medicines and minimize the impact on environment.

- To measure how green is a chemical process, a standard set of 12 principles has been developed. It is a memorable acronym (PRODUCTIVELY)
- E-factor is a particular important parameter for measuring how green a manufacturing process is in terms of the impact it makes on the environment

Genotoxic Impurities – minimize through developing synthetic methods and purification

- Several compounds that possess the potential for genotoxicity have been identified. These toxins if present in the medicines, even in very small quantities could impose health risks
- QbD has been applied to eliminate or minimize the contamination of API's with genotoxic impurities. Every step of the synthesis process can be optimized individually to minimize undesired contaminants.

Pharmaceutical view point:

- Improving biological profile of new medicines**:** From decades of pharmaceutical research, several physic-chemical properties have been identified that improve the biological profile of the medicine.
- Several structural features have been identified that would impart good physic-chemical properties to the drug molecules. Following these findings, drug-like qualities can be designed into the new medicines.

Conclusion

- If academic research groups, pharmaceutical companies and the regulatory agencies work together to implement QbD principles to discovery, development and manufacture of medicines, it will tremendously improve the quality of new medicines reaching the consumer.

Chapter 2

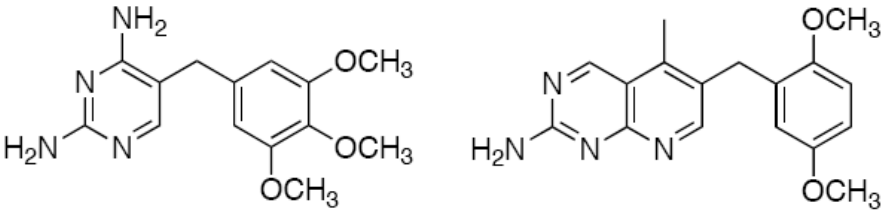
Palladium-Catalyzed Synthesis of Diarylmethanes: A Mechanistic Study

Introduction:

In synthetic chemistry, carbon-carbon bond formation is one of the most important reactions. It is the underlying theme that can be expanded upon to derive important synthetic methods pertaining to organic chemistry. It allows chemists to create known or novel molecules with potential of important physical and biological properties. Several methodologies have been developed for making carbon-carbon bonds, including the Wittig reaction [50], for which the Nobel Prize was awarded in 1979, and the Grignard reaction [51], for which a Nobel Prize was awarded in 1912. A relatively newer approach is the Palladium-catalyzed cross-coupling reaction, which was also awarded the Nobel Prize in 2010 [52]. The need for more of such methods has not yet been attained. So far, chemists have only exploited a very small fraction of the imaginable chemistry space. It is important to continue chemistry research in this field and develop new methods that can tolerate various functional groups and structural moieties in the reactants. This would make synthesis of complicated molecules possible. It is equally important for chemists to understand the mechanism of these reactions. Mechanistic insight into a reaction enables its optimization and the exploitation of its full potential.

The diarylmethane structural motif is found in several biologically active compounds and is incorporated into a number of pharmaceuticals. It is present in antibiotics like

Trimethoprim[53] and Piritrexim [54], whose structures are shown in Figure 1. Trimethoprim is a bacteriostatic antibiotic, which is used in the prophylaxis and treatment of urinary tract infections [53]. It is adihydrofolatereductaseinhibitor. Piritrexim is a lipid-soluble drug which is also an inhibitor of dihydrofolatereductase, which is used for the treatment of the opportunistic infections in AIDS patients. [54].



Trimethoprim (**antibiotic**)

Piritrexim (antibiotic)

Figure 1:The diarylmethane motif is an important structural component of antibiotics.

Therefore, developing new methods for the synthesis of the diarylmethane motif that tolerates various functional groups and structural moieties is always of great importance. There are several methods known for the synthesis of diarylmethanes. Some examples from the literature include palladium-catalyzed cross-coupling reactions of benzylic halides with aryl boronic acids [55], carbon-carbon bond formation via benzylation [56], multicomponent Mannich type Friedel Crafts reaction [57], and the cross-coupling of aryltrifluoroborates with benzyl halides [58,59].Figure 2 presents a novel route to the synthesis of diarylmethanes using the palladium-catalyzed reaction of benzyl bromides and benzyl ketones, developed by Leadbeater et al [60].

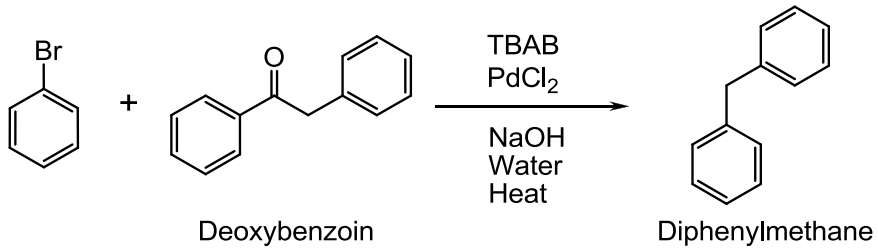


Figure 2: Synthesis of diphenylmethane using the palladium-catalyzed reaction of bromobenzene and deoxybenzoin.

This method avoids the use of transmetallating reagents, thus improving the economy of the reaction [60]. Also, the process is performed in water, making it the method of choice given current emphasis on green chemistry.

Objective:

The goal of this project was to study the mechanism of the Palladium-catalyzed synthesis of diarylmethanes, specifically, the order and the activation energy of this reaction. Leadbeater et al have proposed that this reaction occurs via the formation of a triaryl intermediate by the following mechanism:

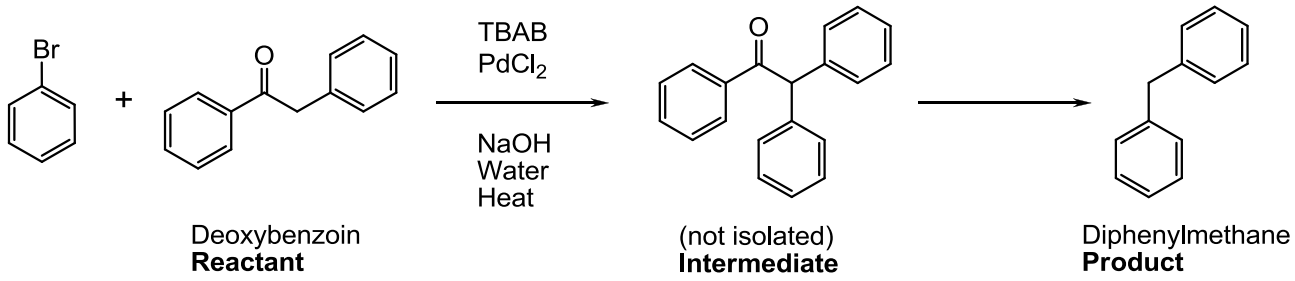


Figure 3: Proposed mechanism of the formation of diphenylmethane from the reaction of deoxybenzoin and bromobenzene via a palladium-catalyzed pathway

They observed the formation of the intermediate during the course of the reaction by NMR (Figure 3). NMR is the most popular spectroscopic technique in chemistry research. It provides information about the number and type of chemical moieties in a molecule. In addition to structural determination, NMR could also be used to determine percentage composition of a mixture of starting materials and products. For this mechanistic study, NMR was very suitable as the analytical technique because the reactant, the intermediate and the product gave three distinct signals; thus all three could be measured quantitatively in the reaction mixture without any separation. In addition, each aliquot taken from the reaction required a short work up before it could be analyzed by NMR [61].Figure 4 shows a typical proton NMR spectrum.

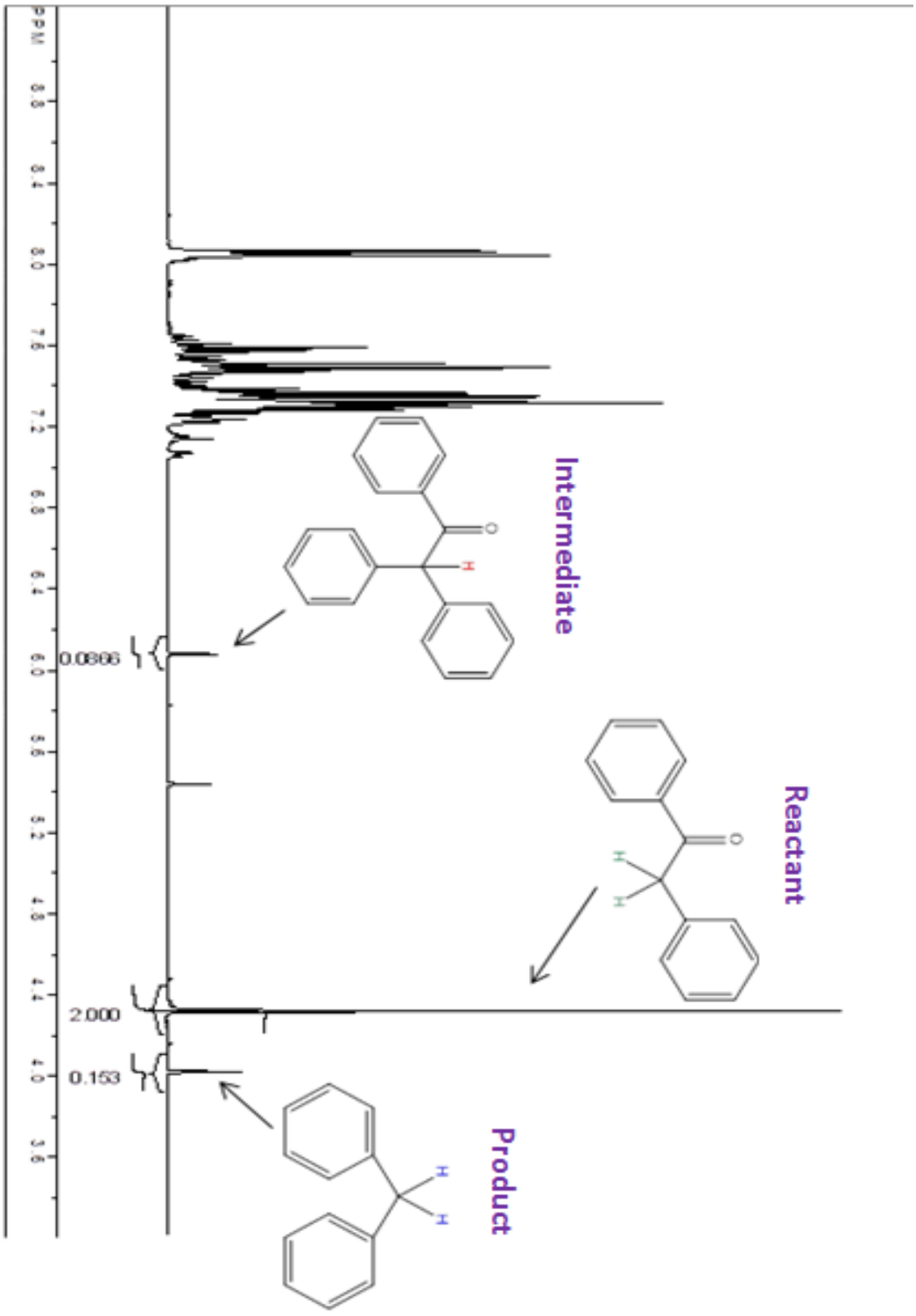


***Figure 4*:** A NMR spectrum showing three distinct integrated peaks representing the intermediate, reactant, and product.

A deeper insight of how this reaction works would allow optimization of the reaction conditions to determine its full potential. Determining the activation energy (E_a) of each step of this reaction, would help in determining the rate determining step (RDS), which then could be optimized to improve the yield of the reaction. The activation energy can be viewed as a "barrier" that must be overcome in order for a reaction to proceed to completion (Figure 4) [62]. Once this energy has been surpassed, the reactant molecules can interact and proceed to form the product. In order to aid the reactant molecules to surpass the activation energy, we can heat the reaction mixture, thereby increasing the kinetic energy of the molecules and allowing them to reach the needed activation energy for the reaction to progress [61].

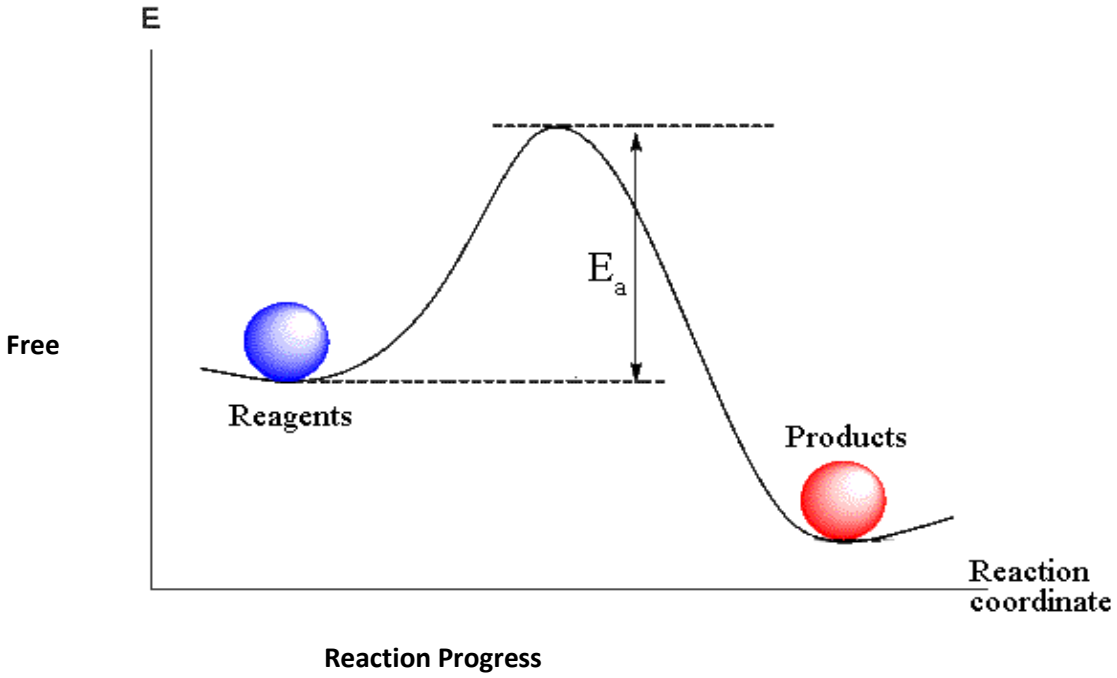


***Figure 5*:** A graphical representation of activation energy in relation to the relative energies of the reagents and products. Figure credited to Belyaev, et al [15].

To determine activation energy, we carried out this reaction at various temperatures and monitored the progress of the reaction by NMR by observing the disappearance of the reactant (deoxybenzoin) as well as the formation of the intermediate (phenyl-substituted deoxybenzoin) and the product (diphenylmethane). The rate equation for a chemical reaction that is of first order with respect to reactant A, at a temperature T, can be written as:

$$\ln[A] = \ln[A]_0 - kT$$

where [A] is the concentration of A at time t, $[A]_0$ is the initial concentration of A (at time t = 0), and k is the rate constant of the reaction at temperature T. We confirmed the order of the reaction with respect to deoxybenzoin to be of first order, by plotting natural log of its concentration against time at different temperatures. Linear plots were obtained at all temperature used, confirming that reaction was of first order. We then determined the rate constants (k) at these temperatures from the slopes of these graphs and calculated the activation energy (E_a) using the Arrhenius equation [62],

$$E_a = -RTlnk$$

where T is the temperature and R is the gas constant.

Methods

This reaction was carried out under the guidance and observation of Jason R. Schmink, using the procedure adapted from his thesis [61].

The reaction was carried out at different temperatures, keeping all other conditions constant. Working on a 5 mmol scale, each of the reactants, deoxybenzoin and bromobenzene, was added to a round-bottom flask, along with sodium hydroxide,

tetrabutylammoniumbromide(TBAB), water, and 1 mol% of the catalyst $PdCl_2$. A Teflon-coated magnetic stir bar was also integrated and the mixture was stirred continuously while being heating in an oil bath. A reflux condenser was attached to the top of the reaction vessel and left open to air. Aliquots were taken at different time points to monitor the progress of the reaction.

Consumption of the reactant (deoxybenzoin) and formation of the product (diarylmethane) was monitored by NMR. Three distinct peaks were observed for the reactant, intermediate, and product in NMR spectra of each aliquot taken. These peaks were then integrated and the values from the spectra of each successive aliquot were used to construct a plot. We plotted ln[deoxybenzoin] vs. time at each reaction temperature. We expected this reaction to be of first order with respect to deoxybenzoin and therefore expected these plots to be straight lines. Characteristic of a first order reaction, absolute value of the slope of the plot will be equal to the rate constant (k).

Next, $E_a$was determined using the Arrhenius equation, which can also be written as:

$$\ln(k) = \ln(A) - \frac{E_a}{R}(\frac{1}{T})$$

Thus a plot between *ln*K and 1/T (called an Arrhenius plot) was determined to be a straight line, with a slope of $-E_a/R$, from which the activation energywas calculated.

Results and Discussion:

The first reaction was done at 95^{o}C, starting from taking aliquots every 15 min, then to every 30 min, and lastly to every 60 min, with a total reaction time of 540 min. NMR spectra of the aliquots were taken to determine the composition of the reaction mixtures at these time

points. Figure 6 plots the results of this experiment. It can be observed that the mole fraction for the product, diarylmethane , increases as the mole fraction for the starting material, deoxybenzoin decreases. A rapid increase in formation of the product is seen, until about 150 min, where the mole fraction of deoxybenzoin and diarylmethane are equal. After this point, the formation of the product begins to slow down. After around 400 min, we see the formation of diarylmethane begin to level off, as the reaction comes to a completion.

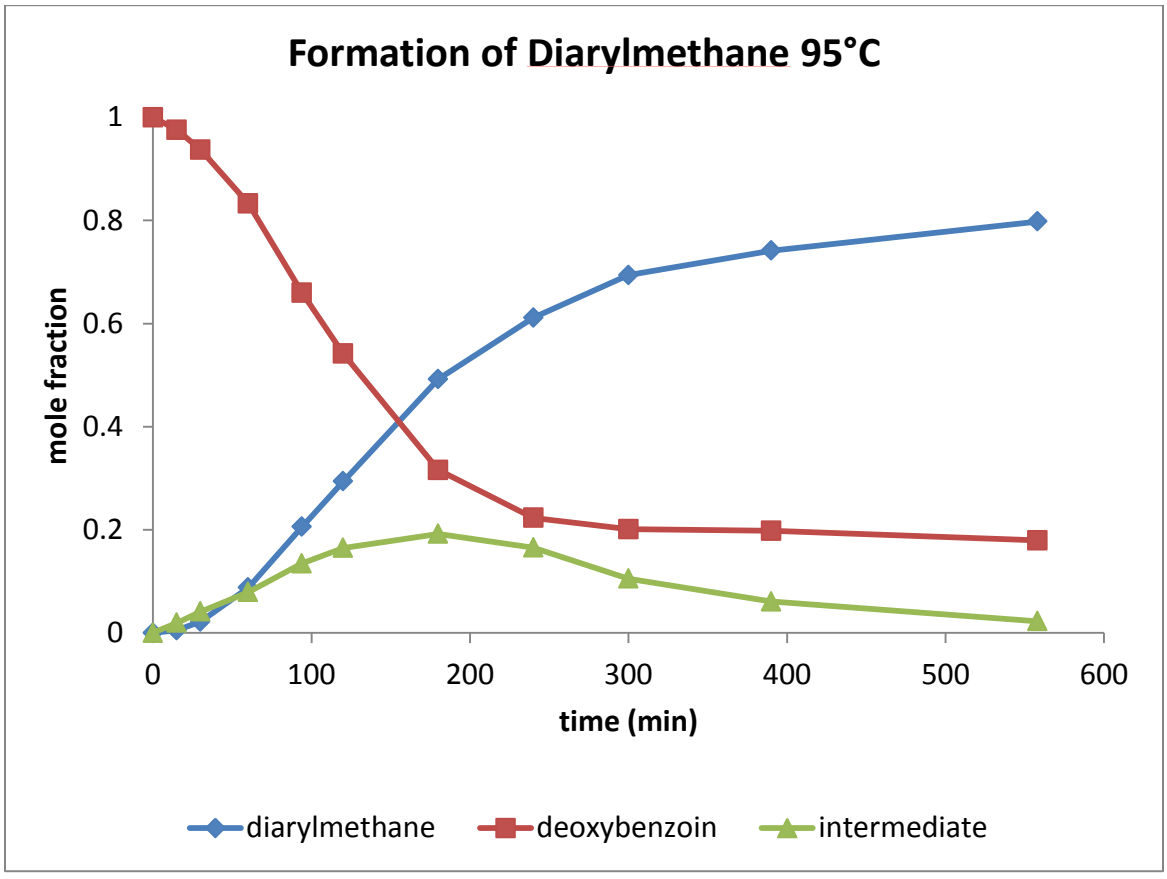


Figure 6: Plot showing the formation of diarylmethane at 95°C. It shows the change in mole fraction of the substrate (deoxybenzoin) with respect to time in min.

Several more trials of the same reaction were conducted, varying only one factor, the temperature. All other variables were kept unchanged. Figure 7 shows a compilation the plots

for each temperature. At each temperature, the natural log of the concentration of deoxybenzoin versus time, in min, is graphed. The almost linear nature of these graphs indicates that the palladium-catalyzed synthesis of diarylmethanes is a first-order reaction with respect to the reactant deoxybenzoin [60]. The slope of each line, representing the reaction conducted at various temperatures, is equal to –k, the rate constant for the reaction at the corresponding temperature, showing that the rate constant increases with increasing temperature.

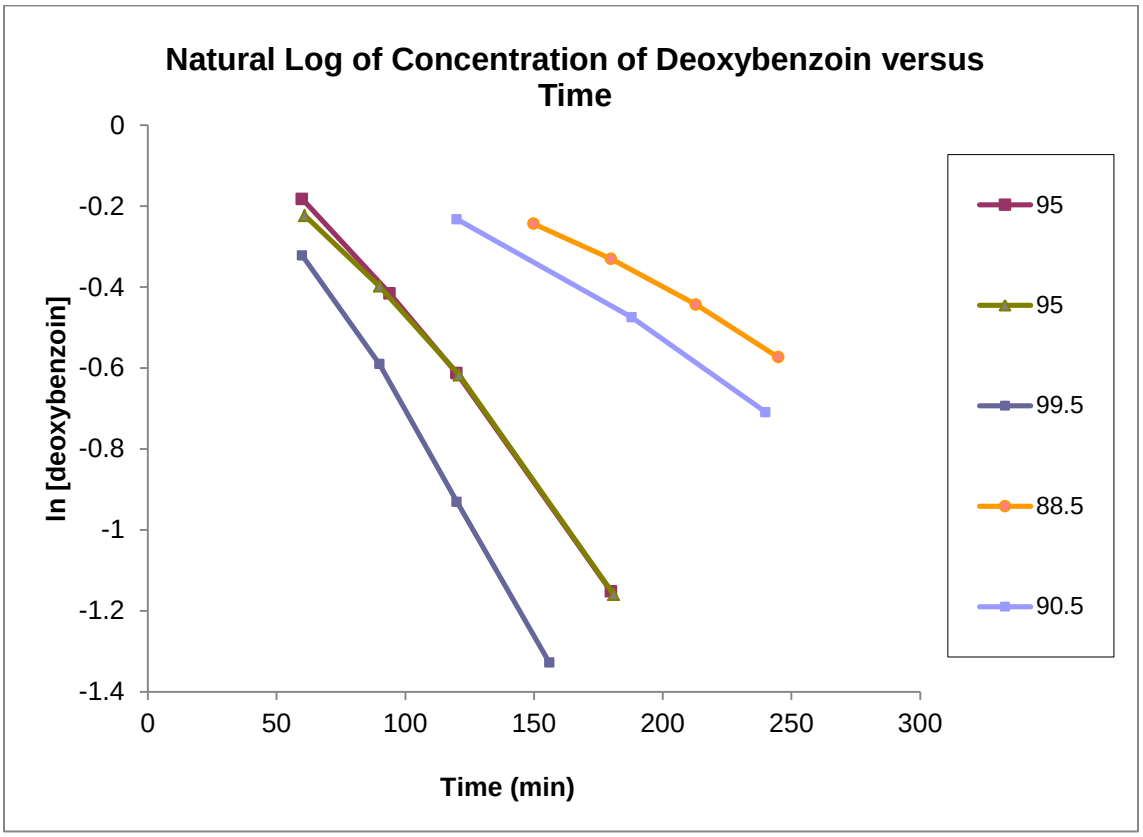


Figure 7:Plot of natural log of concentration of deoxybenzoin versus time (min) at 5 various temperatures ranging from 90°C to 100°C.

Analyzing the data given in Figure 7 at each of the different temperatures, a third plot was constructed in order to calculate the activation energy for the reaction using the Arrhenius equation, given in the methods section. If we graph the natural log of the rate constant versus the reciprocal of the temperature the reaction was conducted at for each of the 5 different temperatures in Figure 7, we obtain the plot given in Figure 8 below. By constructing a best-fit line for this data, we can use the Arrhenius equation to affirm that the slope of this line is equal to $-E_a/R$ and thus calculate the activation energy for the diarylmethane synthesis. As represented in Figure 7, the activation energy of the palladium-catalyzed synthesis of diarylmethane from deoxybenzoin is 123 kJ/mol.

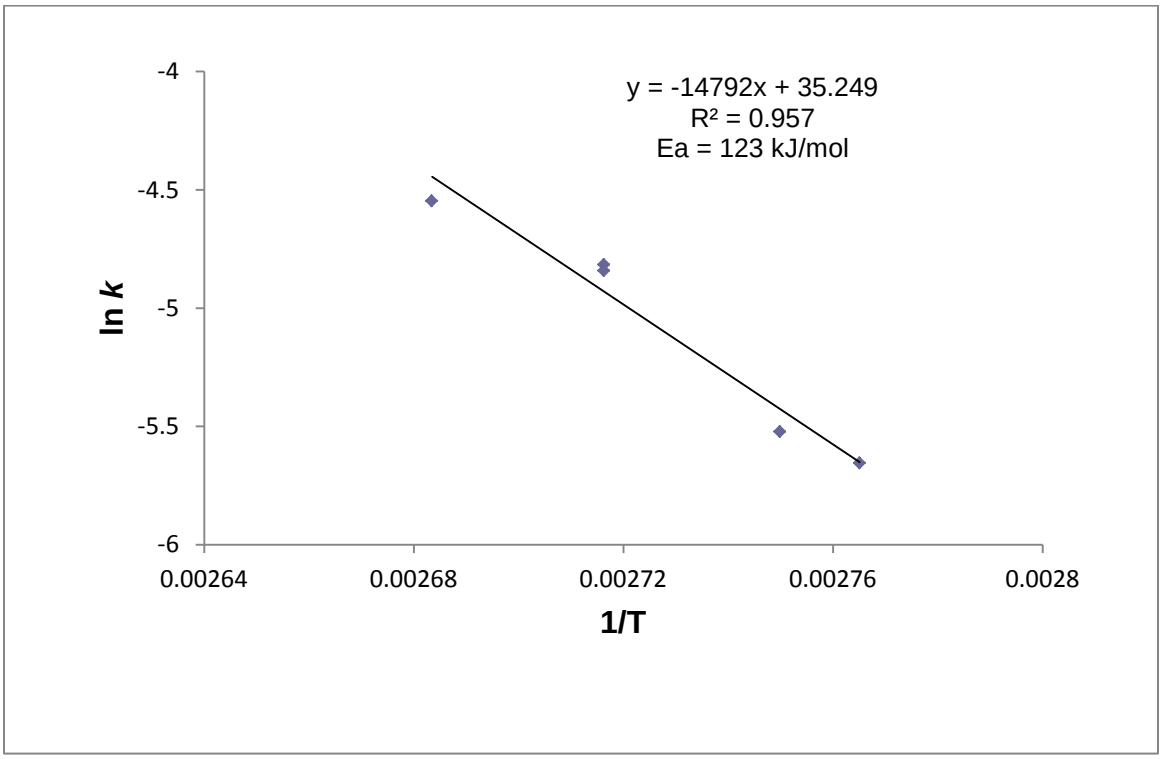


Figure 8: Plot used to calculate activation energy (E_a). Graphs natural log of rate constant (k) versus the reciprocal of the temperature in Kelvin.

Future Goals

To continue with this project, we plan to study the specific step of the reaction, when the intermediate changes to the product. We will study the reaction at different temperatures and calculate the activation energy for this specific step of the reaction mechanism. This will help us determine exactly which step of the mechanism is the rate-determining step as it will have the highest activation energy. Furthermore, optimization of the rate-determining step can be done to improve the yield of the overall reaction.

Chapter 3

The Optimization of Microwave-Assisted Click Reactions and Suzuki Couplings for Use in an Undergraduate Organic Chemistry Laboratory Manual

Introduction:

The aim of this chapter was to help develop experiments for a new undergraduate laboratory manual for organic chemistry. The experiments in this manual were all performed using microwave heating. Synthesis of organic materials using microwave heating can provide several advantages as will be discussed later. By developing this new manual, we hoped to add new reactions and concepts to the undergraduate organic chemistry laboratory experience such click chemistry and Suzuki coupling. One example of each of the reactions was performed under varying reaction conditions and procedures were perfected. Product yield was confirmed by using an internal standard and analyzing the product using NMR spectroscopy. NMR was also be used to confirm the identity of the product.

Microwave-Assisted Synthesis and its Advantages

The energy source and the method of its delivery can greatly influence the outcome of a chemical reaction [63]. Microwaves have become an important tool for providing energy for molecules in a reaction. This method of providing energy has been applied to inorganic chemistry reactions since the late 1970s and to the field of organic chemistry only since the mid-1980s [64].

An advantage of using microwave irradiation as a source of energy is that it provides direct energy to the reactant molecules of interest and this energy can be applied in a controlled manner [63].This means that it can decrease the reaction time because instead of just heating the surface of the container holding the reaction mixture, microwave irradiation provides energy to the molecules directly. Before microwave heating became a popular technique, conventional heating techniques were used. These techniques were successful in that reactions could be completed using an oil bath or hot plate, however there were not energy efficient. More time and wasteful amounts of energy were required to first penetrate the surface of the reaction vessel in order to even reach the reactant molecules. Using microwave heating, energy is not wasted heating the walls of the reaction vessel, solvent surrounding the reactant molecules, but instead energy is directed only where it is needed and where it can have full effect in running the reaction to completion, turning the reactant molecules to product. Microwave irradiation is a much greener method because it can provide direct energy to the reactant molecules and therefore uses less energy than conventional methods to provide the same effect.

Microwave energy allows for the more rapid heating of reaction mixtures to high temperatures and subsequently a more rapid cool down. This allows for less solvent needed for the reaction to run to completion, which means that the reaction mixture requires a quicker work-up after completion. Furthermore, newly developed microwaves used in laboratories today make it easier to adjust and record the time, temperature, and power used during each microwave run [63]. In this way, microwave heating can provide precise process control. Finer adjustments can be made to the temperature, run time, and power and these can almost immediately take

effect. Fine tuning the reaction conditions can provide for quicker results and therefore one can perfect reaction conditions with more efficiency and careful precision.

Overall, using microwave heating provides for significant reaction rate enhancement, reduced overall process time, increased product yield, improved product purity, and high reproducibility, as compared to employing conventional heating methods such as heating this reaction mixture in an oil bath, steam bath, or on a hot plate. Therefore, microwave-assisted organic synthesis has led to many critical advancements in the field of greener chemistry by making a vast number of synthetic methods cleaner, faster, and more robust [64].

This thesis addresses the use of microwave heating in two organic synthesis reactions, including the formation of triazoles through click chemistry and carbon-carbon bond forming Suzuki coupling reaction. These reactions show how microwave irradiation can be used for a variety of reactions, including those forming heterocyclic rings and those requiring metal catalysts.

Click Chemistry: The Formation of Triazoles

In the last ten years there has been an increased interest in click chemistry, beginning with the publication from Sharpless et al.[65]. The concept of click chemistry is inspired by nature's way of generating substances quickly and reliably by combining small units for example all proteins are created from 20 building blocks (amino acids). Nature has a preference for making carbon-heteroatom bonds over carbon-carbon bonds. Synthesis of polysaccharides, nucleic acids and proteins are a result of condensation of polymers of subunits via carbon-heteroatoms [66]. Sharpless et al [65] have defined a criterion that a reaction must meet to be characterized as a click reaction. Several reaction schemes that meet the requirements of click chemistry are shown in Figure 1.

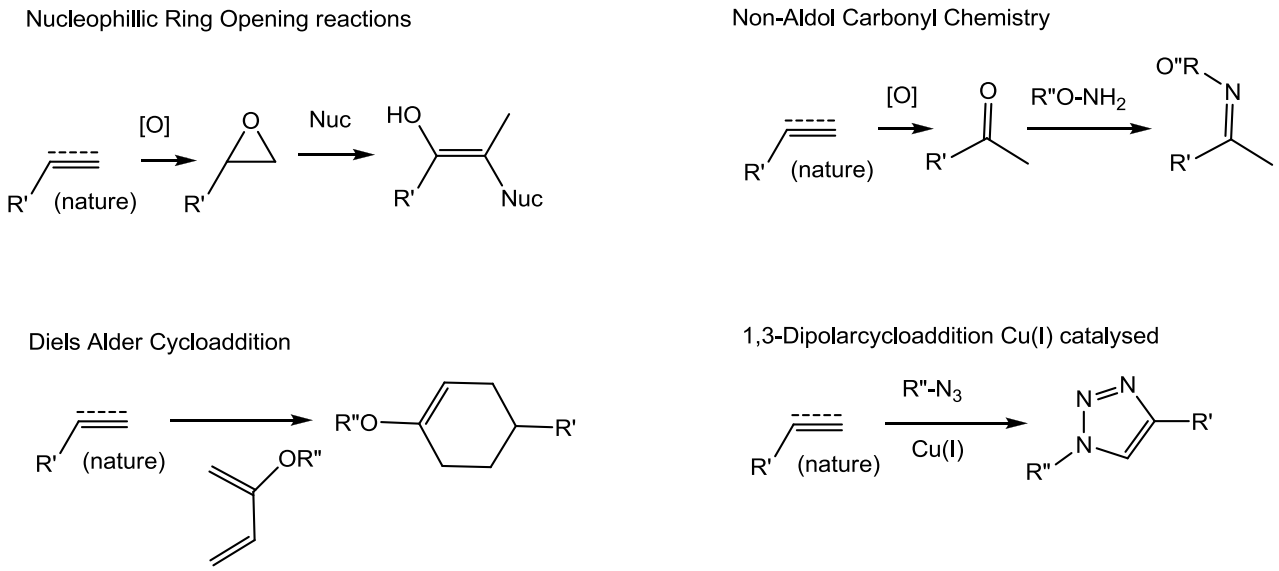


Figure 1: Click Chemistry Reaction Schemes

The most prominent click reaction is the 1,3-dipolar cycloaddition of alkynes and azides to yield 1,2,3-triazoles. In the absence of a transition-metal catalyst, this reaction is not regioselective, and requires high temperatures. In 2002 two separate groups[67,68] reported that catalytic amount of Copper(I), which can bind to terminal alkynes leads to fast and regioselective cycloaddition to azides at room temperature in organic medium (Figure 2). A wide variety of functional groups and reaction conditions are tolerated. This new reaction process requires no protecting groups, and proceeds with almost complete conversion and selectivity for the 1,4-disubstituted 1,2,3-triazole (anti-1,2,3-triazole). No purification is generally required.

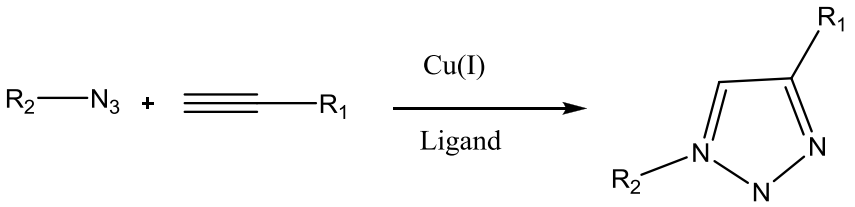


Figure 2: Regioselectiveazide-alkyne coupling

The proposed mechanism of this reaction is shown in Figure 3[69]. Based on earlier precedent of CuI (copper iodide) insertion into terminal alkynes and experimental data showing that internal alkynes are not reactive a stepwise catalytic cycle beginning with formation of a Cu-acetylide complex is proposed. Azide displacement of one ligand produces a copper-acetylide-azide complex followed by cyclization results in a metallocycle which undergoes ring contraction to give the triazole-copper complex. Protonation of this complex gives the triazole and regenerates the catalyst.

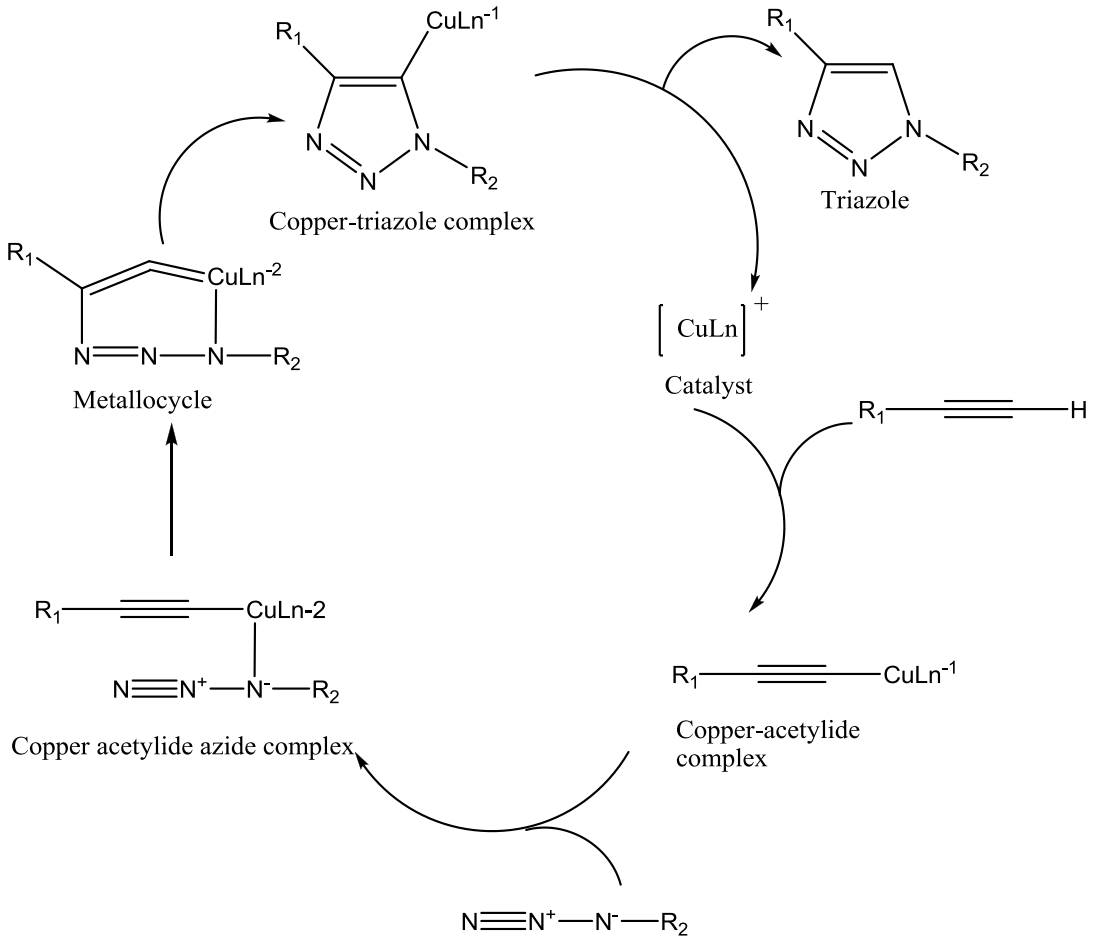


Figure 3.Proposed mechanism of Triazole formation.

The use of microwave heating can improve the alkyne-azide coupling by reducing reaction times and facilitating one-pot reactions [70]. The latter allows access to volatile and unstable azides, which can are prepared in-situ giving new triazoles not available by traditional methodologies [71]. In general, use of microwave conditions show similar substituent effects, inertness to functional groups, and yields [72]. In cases where the triazoles have solubility issues in aqueous reaction conditions, good yields are observed by using organic solvents under microwave conditions.

Objective

The goal for this section was to optimize the procedure for the synthesis of 1-phenyl-2-(4-phenyl-[1,2,3]triazol-1-yl)-ethanone from 2-bromoacetophenone, phenyl acetylene, and sodium azide for the design of an undergraduate organic chemistry lab manual.

Methods:

When designing the organic chemistry laboratory manual, the first reaction considered was the synthesis of a triazole using click chemistry. Working on a 2 mmol scale, 2-bromoacetophenone, phenyl acetylene, and sodium azide, were combined in an equimolar solution of *tert*-butanol and water. An aqueous solution of copper (II) sulfate pentahydrate was also added as catalyst. This reaction is represented by Figure 4 below.

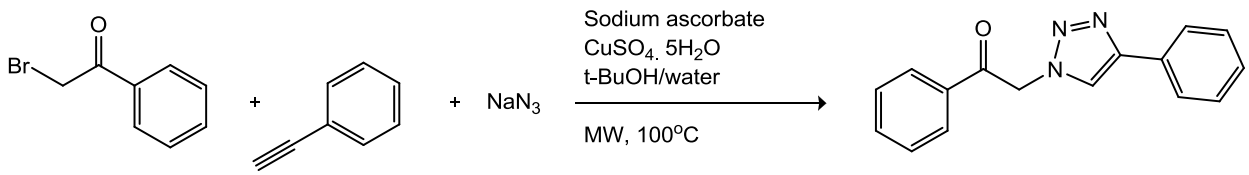


Figure 4: Click reaction of 2-Bromoacetophenone, phenyl acetylene, and sodium azide for the synthesis of 1-phenyl-2-(4-phenyl-[1,2,3]triazol-1-yl)-ethanone

This reaction was conducted in the microwave, varying only the reaction time and temperature, in order to obtain the maximum yield for the reaction. After each trial, the reaction mixture was poured into an ice bath and aqueous ammonia was added. The solid precipitate was then collected using a Buchner funnel and air dried overnight. The identity of the product was confirmed using proton NMR spectroscopy, and product yield was determined by weighing. For a more detailed account of the protocol, please refer to section A.3a of the Appendix of this thesis.

Results and Discussion

A protocol was obtained from the CEM Laboratory Manual for microwave assisted in organic chemistry for the synthesis of of 1-phenyl-2-(4-phenyl-[1,2,3]triazol-1-yl)-ethanone from 2-bromoacetophenone, phenyl acetylene, and sodium azide, using conventional heating techniques, and this procedure was adapted so that it could be performed using microwave irradiation as the heat source [73]. The microwave conditions were optimized by running three trials of the reaction, adjusting only the reaction time and temperature with each run, and obtaining a yield for the reaction.

Product identification was carried out using NMR. The NMR for the triazole product of this reaction is given in section A.3a of the Appendix. Percent yield for each of the trails was obtained by weighing the dried product and comparing it to the theoretical yield (0.5309 grams) for this reaction. The first trial was conducted at 70^{o}C for 30 min. With these reaction conditions only a 53 % yield (0.2805 grams) was obtained. In the second run of the experiment

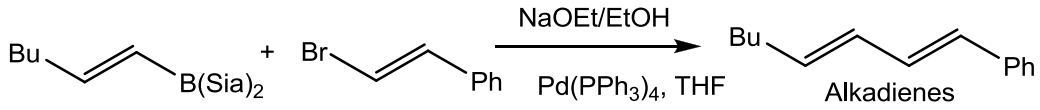
the reaction temperature was increased to 130^{o}C, but the reaction time was shortened to 20 min. This trial gave a yield of 62 % (0.3269 grams). The last trial obtained the highest yield overall. This trial was conducted at 100^{o}C for 10 min and a 66 % yield (0.349 grams) was obtained.

Microwave-Promoted Suzuki Coupling

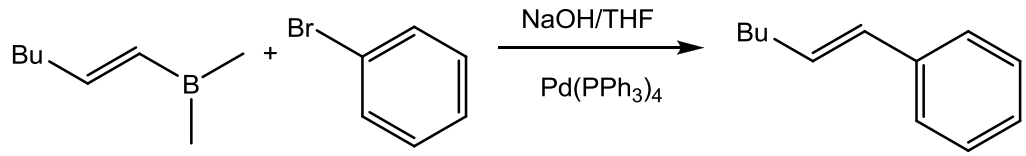
Carbon-carbon bond forming reactions are important as they are key in synthesis of complex molecules. Transition metals have been used to mediate these reactions. Suzuki coupling is the most widely used reaction for forming C-C bonds. It is the palladium catalyzed reaction between organo boron compounds and halides or triflate in the presence of a base [74]. The sp, sp2 and sp3 carbon-boron compounds can be used in the cross-coupling. Examples of each of these are shown in Figure 5. [75][76][77][78]

Coupling Reactions of sp2 Carbon-Boron Compounds

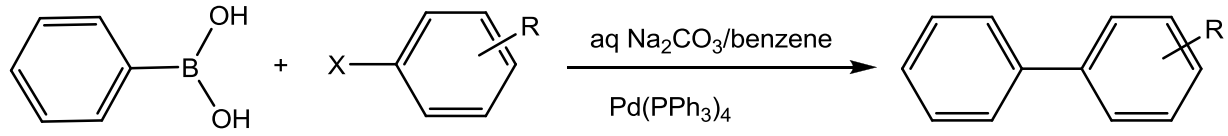
Reactions of Vinylic Boron Compounds with Vinylic Halides



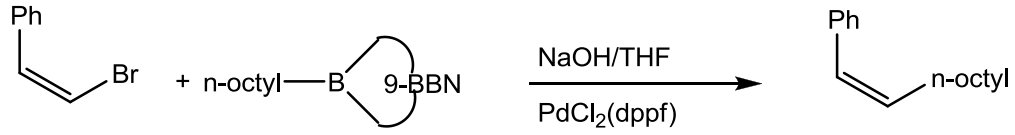
Reactions of Vinylic Boron Compounds with Aryl Halides



Reactions of Aryl Boron Compounds with Aryl Halides



Coupling Reactions of sp3 Carbon-Boron Compounds



Coupling Reactions of sp Carbon-Boron Compounds

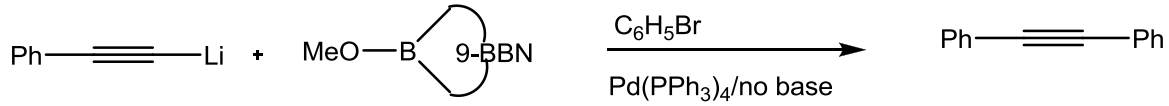


Figure 5. Representative reactions of various organoboranes.

The main advantages of the Suzuki coupling is its tolerance of several functional groups, mild reaction conditions and water stability. In addition the boronic acids used are known for their

stability, ease of handling and commercial availability. Mechanism of the reaction is shown in Figure 5. It involves a catalytic cycle where the first step is the oxidative addition of an aryl halide to palladium(0) to form an aryl palladium (II) halide intermediate. This intermediate is next transmetalated with a boronic acid followed by reductive elimination to give the biaryl product and restoring the Pd(0) complex.

The palladium catalysts used in the Suzuki coupling have ligands attached to the Pd atom. These ligands are organic groups. In the early work triarylphosphines were used as catalysts. In recent years new bulky and electron-rich phosphine ligands have been discovered which has improved efficiency of these coupling reactions.[79]

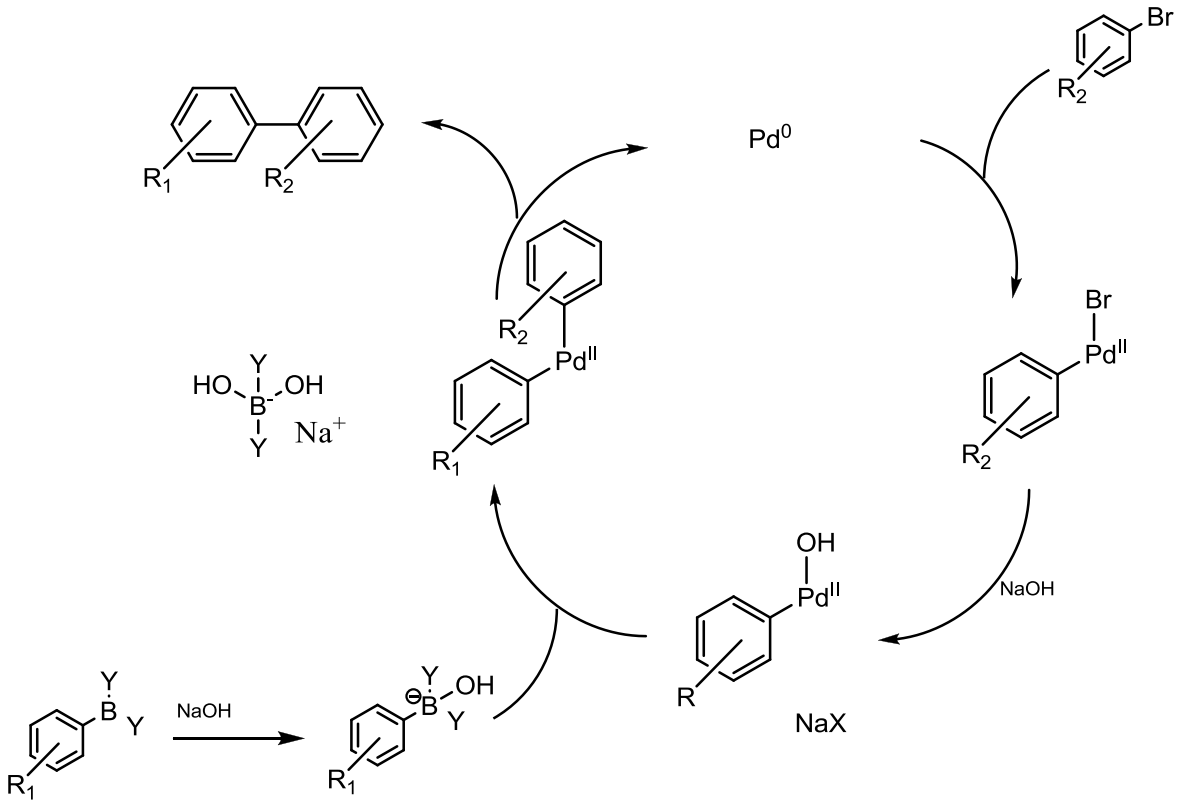


Figure 6.Mechanism of Suzuki Reaction [75].

Mineral bases such as alkali metal carbonates or K_3PO_4 are used as bases in the Suzuki reactions. The use of water as an additive helps in solvation of the inorganic bases. Several research groups have studied reaction conditions to make this reaction more environmentally favorable by using water as a solvent or trace quantity of catalysts. [80,81] Researchers have successfully used water as solvent for Suzuki reactions. The addition of one equivalent of phase transfer catalyst (PTC) tetrabutylammonium bromide (TBAB) to the reaction mixture greatly accelerates the reaction, poly(ethylene glycol) has also been used as a PTC. Using water soluble aryl halide and boronic acid components requires no phase-transfer agent is required.[82] Leadbeater's group [80] has shown that Suzuki-type coupling methodology does need a catalyst but that it can be performed with sub-ppm levels of palladium. His group has also combined two techniques, use of water as a solvent and application of microwave heating (for efficient heating of reaction mixture) to make the Suzuki reaction faster easier and cleaner.

Objective:

The goal for this section was to optimize the procedure for the synthesis of biphenyl from bromobenzene and phenylboronic acid for the design of an undergraduate organic chemistry lab manual.

Methods:

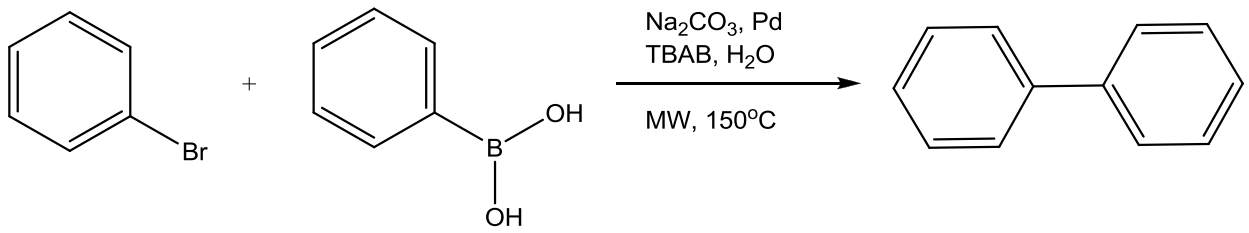


Figure 7:Suzuki Coupling of bromobenzene and phenylboronic acid for the synthesis of biphenyl.

When designing the organic chemistry laboratory manual, the first reaction considered was the Suzuki coupling of bromobenzene and phenylboronic acid to form biphenyl, as shown in Figure 7. The solvent used for this reaction was TBAB and the reaction was catalyzed using an ICP standard, a catalytic palladium solution. It was conducted in the microwave for five min at 150^{o}C. An ethyl acetate work up was performed and the final product was rinsed with brine to isolate the product, diarylmethane. The identity of the product was confirmed using proton NMR spectroscopy. The addition of an internal standard allowed for the calculation of percent yield for the reaction as well. For a more detailed account of the protocol, please refer to section A.3b of the Appendix of this thesis.

Results and Discussion

The Suzuki coupling reaction performed was the formation of biphenyl from bromobenzene and phenylboronic acid. A protocol was obtained from the CEM Laboratory Manual for microwave assisted in organic chemistry for the synthesis of 4-acetylbiphenyl from phenylboronic acid and 4'-bromoacetophenone and was adapted for this reaction [73]. This procedure was optimized for microwave power by running three trials of the reaction at two microwave powers, 150 and 200 Watts, anddetermining the yield of the product for each run. Both yield assessment and product identification was carried out using NMR. Percent yield for each of the trails was obtained by adding a known amount of an internal standard and comparing peak integration values for the product with those of the internal standard. The internal standard used was 1, 2, 4, 6-tetramethylbenzene, which shows a singlet for 12 protons with chemical shift of about 2.1 ppm in the proton NMR. The NMR for the product, biphenyl,

for this Suzuki coupling reaction is shown in section A.3b of the Appendix. For the trial with a power of 200 Watts, the yield of the product biphenyl was 23 %. The other two trails were ran with a power of 150 Watts. An average yield of 64 % was obtained from these two runs. These results suggest that this Suzuki coupling microwave power of 150 Watts produces better results than the 200 Watts.

Chapter 4

In-Situ Reaction Monitoring using Raman Spectroscopy: Bobbitt Oxidation

Introduction:

N-oxoammonium salts oxidize alcohols to aldehydes and ketones. They are quite selective for the oxidation of alcohols. N-oxoammonium salts could be used in stoichiometric amount or catalytic quantities, where NaOCl is the ultimate oxidation source [83]. In this section of the thesis, we describe our attempt to study the progress of microwave-assisted Bobbitt oxidation of benzhydrole to benzophenone by using Raman spectroscopy. Microwave-assisted reactions have become very popular because they are very convenient to do and reaction conditions like temperature and duration could be controlled easily and precisely (described in greater detail in Chapter 3). Raman spectroscopy was selected as the analytical tool because, a microwave reactor can be coupled to a Raman spectrometer quite conveniently and Raman spectra can be acquired straight from the microwave reaction vessel without the need to remove it from the microwave cavity or take an aliquot.

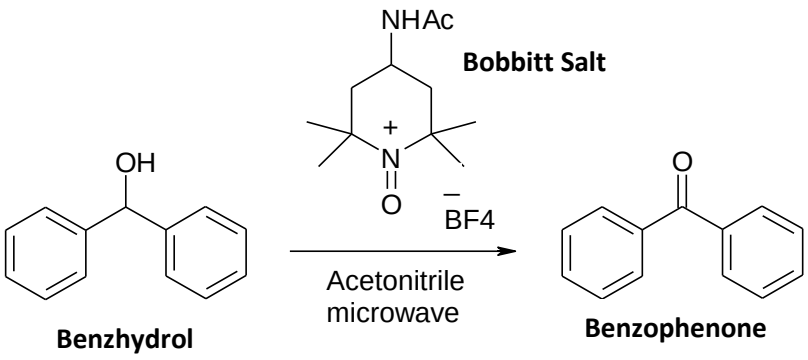


Figure 1: Bobbitt oxidation

Raman spectroscopy:

Raman spectroscopy is a spectroscopic technique which measures vibrational and rotational modes of molecules. It is complementary to infrared spectroscopy, which also relies on vibrational and rotational transitions through the direct absorption of incident electromagnetic radiation. In IR spectroscopy, polar bonds, e.g. C=O bond a carbonyl, are visible and non-polar bonds, e.g. symmetrical C=C double bonds, are transparent. Raman spectroscopy on the other hand involves two steps. In the first step the incident radiation polarizes the molecules and excites them to a virtual state. In the second step, the photons of the incident radiation collide with these excited molecules and get scattered with a different energy. These scattered photons with vibrational information of the molecule are detected. Thus in Raman, vibrational modes of symmetrical bonds can be detected [84].

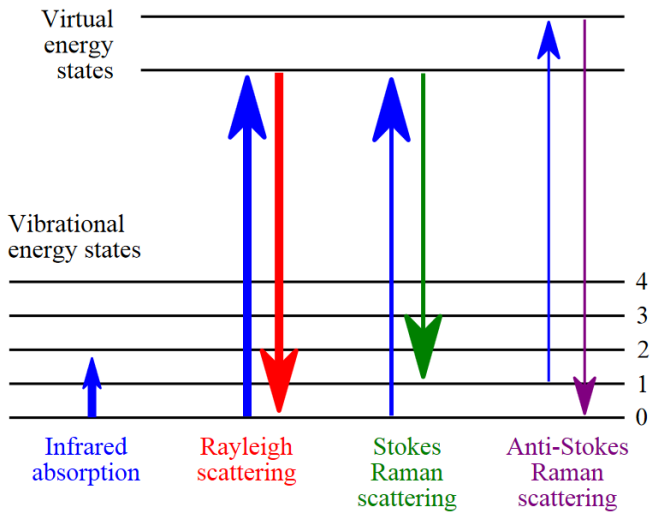


Figure 2: Raman Spectroscopy

Drawbacks of Raman spectroscopy: Since Raman spectroscopy depends on the detection of scattered photons from collisions with the molecules being studied, scattering from any other particles would interfere. To avoid that the medium being studied should be completely clear. Another drawback in this spectroscopy is that Raman transitions have very low probability, giving very weak signals. Several technical advancements have been made to improve the sensitivity of Raman spectroscopy, e.g. longer detection durations, but that discussion is out of the scope of this thesis.

Advantages of Raman spectroscopy: Probably the biggest advantage to use Raman spectroscopy to study kinetics of a reaction is that borosilicate glass is completely transparent to Raman. This allows taking true *in vivo* Raman spectra of a reaction directly from the reaction vessel, without any invasive needs of taking an aliquot, etc. Also, a Raman spectroscope could be very conveniently coupled to a microwave reactor [85]. Microwave reactors are closed systems, in which heating would need to be paused if a sample needs to be taken. Some models of lab-microwaves have been equipped with a side port giving access to the microwave cavity, where a probe could be inserted and placed right next to the reaction vessel (Figure 3). Through this setup, in the Leadbeater lab, a Raman spectrometer is coupled to a microwave reactor by inserting a quartz light pipe (a Raman probe) through the side port of the microwave. It places the end of the light pipe probe right next to the reaction vessel allowing acquiring in-situ Raman spectra of the reaction. This setup constitutes a near-perfect technique to study a microwave-assisted reaction via Raman spectroscopy [86]. For this series of experiments, the CEM S-class scientific microwave was interfaced with a Raman spectrometer

from Enwave Optronics, as shown in Figure 3. The instrumentation was set up in collaboration with a graduate student [61].

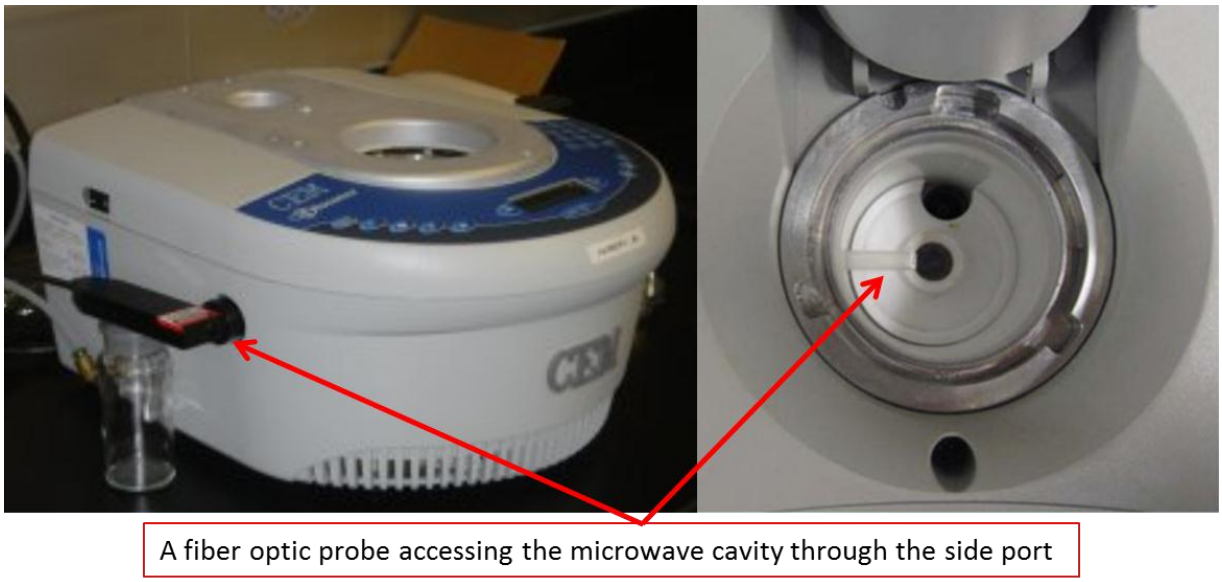


Figure 3: A microwave reactor with a Raman light pipe placed right next to the reaction vessel [61].

Results and Discussion

We applied the Raman-microwave interface technique to the oxidation of benzhydrol to benzophenone, using Bobbitt's salt, an oxoammonium salt. All work using the microwave and Raman instrumentation and analysis of the Bobbitt oxidation reaction was done under in collaboration with a graduate student (Acknowledgements). First a dark scan was taken, followed by a background scan. The background scan was subtracted from each following scan taken, in order to ensure minimal background noise be incorporated with each scan.

The Raman spectra of the starting material, benzhydrol, and of the product, benzophenone, were identical, as shown in Figure 4. Therefore, we were unable to measure the progress of the

reaction using Raman spectroscopy. Separately, the completion of the reaction was confirmed using NMR spectroscopy.

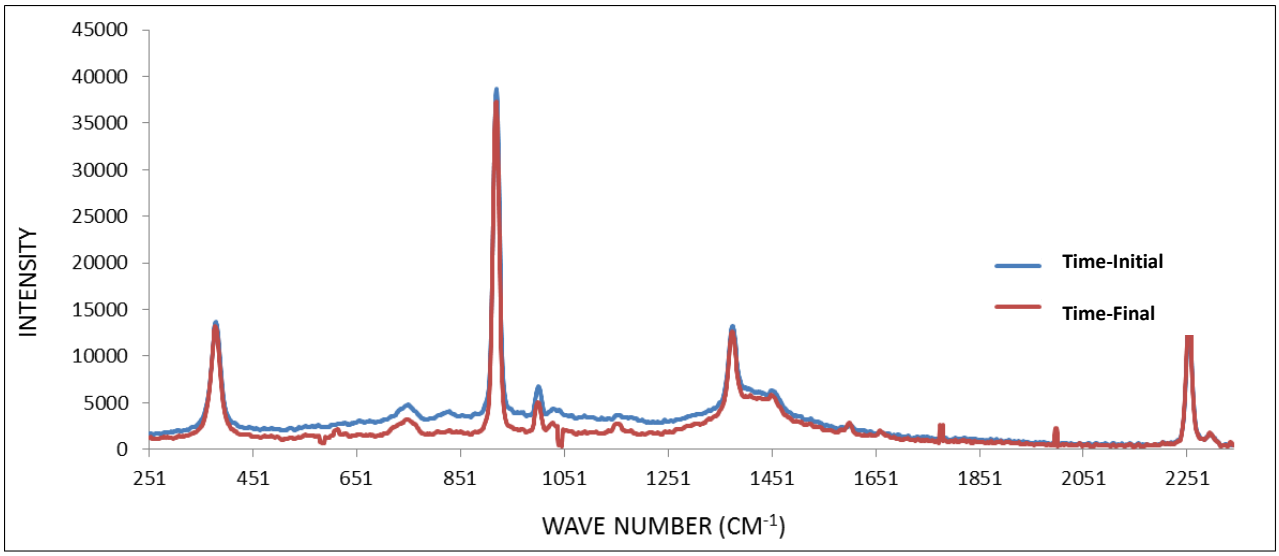


Figure 4: The Raman spectra of the reactant, shown in blue, and the product, shown in red.

One possible explanation for the identical Raman spectra is that in Raman spectroscopy stretching of symmetrical bonds are seen, while polar bonds are almost transparent. In the reaction we studied, oxidation of benzhydrol to benzophenone, the symmetrical bonds of the reactant and product essentially remained unchanged during the reaction. Though the carbonyl group in the product might change the vibrational energy of the bonds in the phenyl groups through resonance, but this change was not enough to be captured using Raman spectroscopy. Another possible reason for this observation can be explained by a disadvantage of employing Raman spectroscopic techniques. The probability of Raman transitions is itself very small, giving a weak signal, which could get lost in the background noise. More modified Raman

spectroscopic techniques, which increase the sensitivity of Raman, could be helpful; however, this is beyond the scope of this thesis.

Appendix

General:

All chemical transformations requiring inert atmospheric conditions utilized Schlenk line techniques with a 3- or 4-port dual-bank manifold. Nitrogen was used to provide such an atmosphere. ^{1}H-NMR Spectra were performed at 298 K, in either $CDCl_3$ or DMSO-d6, on either a Brüker Avance Ultra Shield 300 MHz NMR, Brüker DRX-400 400 MHz NMR, or Brüker Avance 500 MHz NMR. ^{1}H-NMR Spectra were referenced to residual non-deuterated chloroform (7.26 ppm) or DMSO (2.5 ppm) in the deuterated solvents. Microwave assisted reactions were carried out in the Discover CEM SP Class microwave (Model No. 909150). When Raman spectroscopy was used to monitor microwave assisted reactions, a Raman spectrometer (EnwaveOptronics) coupled with a Discover CEM S Class apparatus (Model No. NP-1008) was used.

A.2: Mechanistic Study of the Palladium-Catalyzed Synthesis of Diarylmethanes (Chapter 2)

Detailed Procedure of the Formation of Diphenylmethane from the Reaction of Deoxybenzoin and Bromobenzene via a Palladium-Catalyzed Pathway

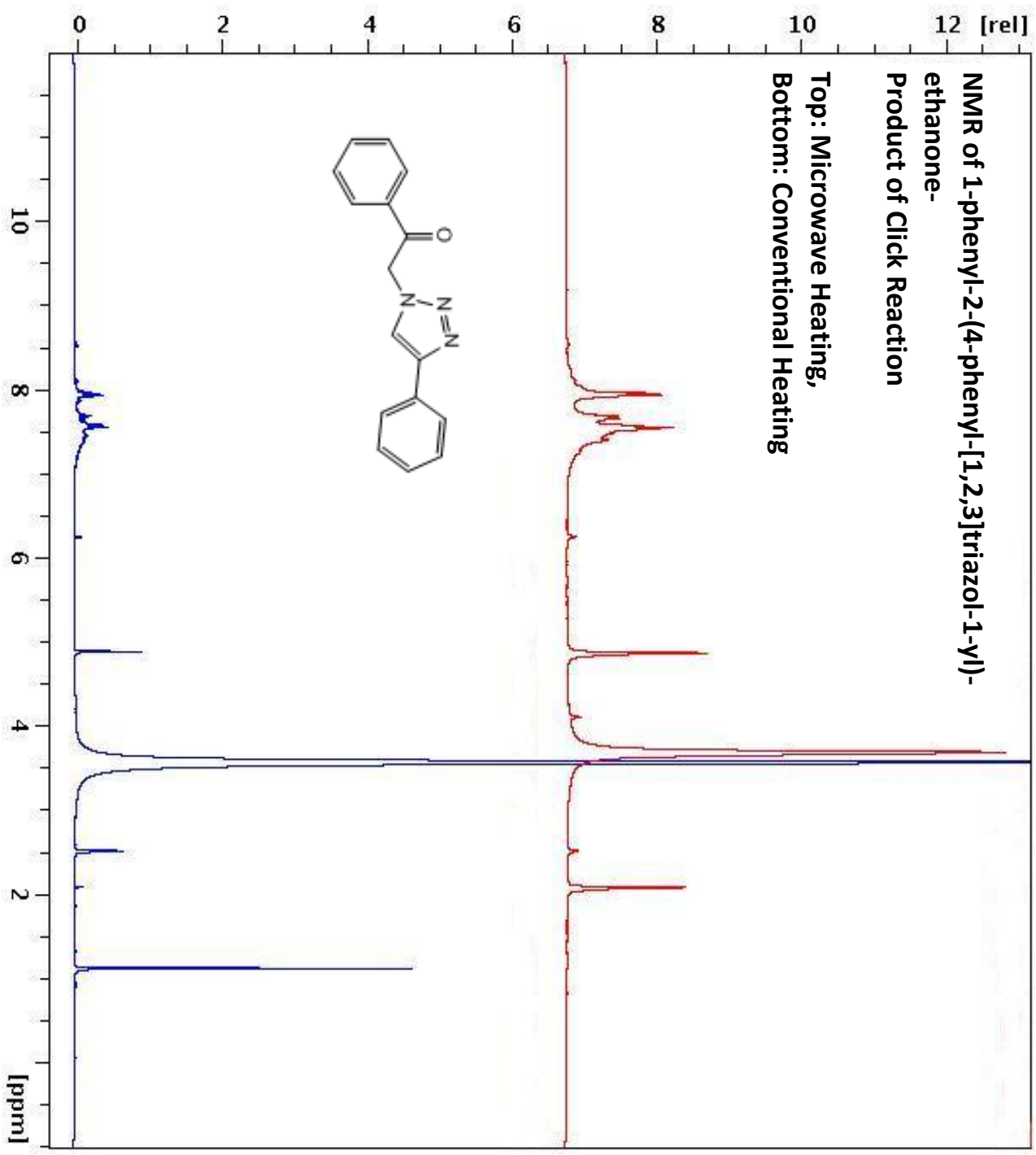
Deoxybenzoin (5 mmol, 981.3 mg), bromobenzene (5 mmol, 785 mg), TBAB (2.5 mmol, 806 mg), 10 mL NaOH, and 3 mL of water were added to a 25 mL round bottom flask. The flask was placed in an oil bath set to approximately 7 to 8^{o}C above the temperature the reaction is being run at. A Teflon-coated magnetic stir bar is added and a reflux condenser is attached onto the reaction vessel, which is left open to the air. The catalyst, $PdCl_2$ (1.0 mol %, 8.8 mg), was also added after approximately 10 minutes. Aliquots were taken at different time points to monitor the progress of the reaction, at 15-minute time points for the first one hour, 30-minute time points for the next two hours, and lastly one-hour time points for the last six hours. The reaction was run for a total of 540 minutes (9 hours). An NMR was taken for each of the aliquots and using peak integration ratios of the reactant, intermediate and product, a graph showing the formation of diarylmethane (mole fraction) with respect to time was constructed (Chapter 2, Figure 6). The peak area for the reactant, deoxybenzoin (at approximately 4.25 ppm) diminished with each consecutive aliquot, while the peak for the product, diarylmethane (at approximately 4.0 ppm) rose. It was also observed that a peak at approximately 6.1 ppm, for the intermediate species, rose as the reaction began and then diminished with the completion of the reaction.

*Procedure is credited to Jason R. Schmink, Ph.D (University of Connecticut)

A.3a: Click Chemistry- Formation of Triazoles (Chapter 3)

Detailed Procedure of the Synthesis of 1-phenyl-2-(4-phenyl-[1,2,3]triazol-1-yl)-ethanone from 2-Bromoacetophenone, Phenyl Acetylene, and Sodium Azide

2-Bromoacetophenone (398 mg, 2 mmol), phenyl acetylene (204 mg, 2 mmol) and sodium azide (136.5 mg, 2.1 mmol), were mixed with 3 mL of *tert*-BuOH/water (1:1) solution in a 10 mL capacity glass microwave reaction vessel containing a magnetic stirring bar. Sodium ascorbate (39.6 mg) and aqueous cupric sulfate pentahydrate (100 uL of 1M solution) were added sequentially. The reaction vessel was sealed with a septum and then placed into the microwave cavity. The pressure device was put in to place on top of the reaction vessel and the unit was programmed to heat the reaction mixture with stirring to 100^{o}C, using an initial microwave power of 150 W and holding at this temperature for 10 minutes. After the reaction was complete and the reaction mixture had cooled to at least 50^{o}C, it was ensured that there is no remaining pressure in the reaction vessel before removing it from the microwave cavity. The mixture was then poured into 10-20 mL of ice water followed by the addition of 5 mL of 10% aqueous ammonia. After stirring for another 5 min, the solid precipitate was collected by filtration using a Buchner funnel and air-dried overnight to give 1-phenyl-2-(4-phenyl-[1,2,3]triazol-1-yl)-ethanone (0.349 g; 65.7% yield). The chemical structure of the product is confirmed by ^{1}H-NMR spectroscopy.NMR of 1-phenyl-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethanone: ^{1}H NMR (DMSO, 400 MHz) δ ppm 8.0 - 7.8 (m, 4H), 7.75 – 7.5 (m, 7H), 4.8 (s, 2H).

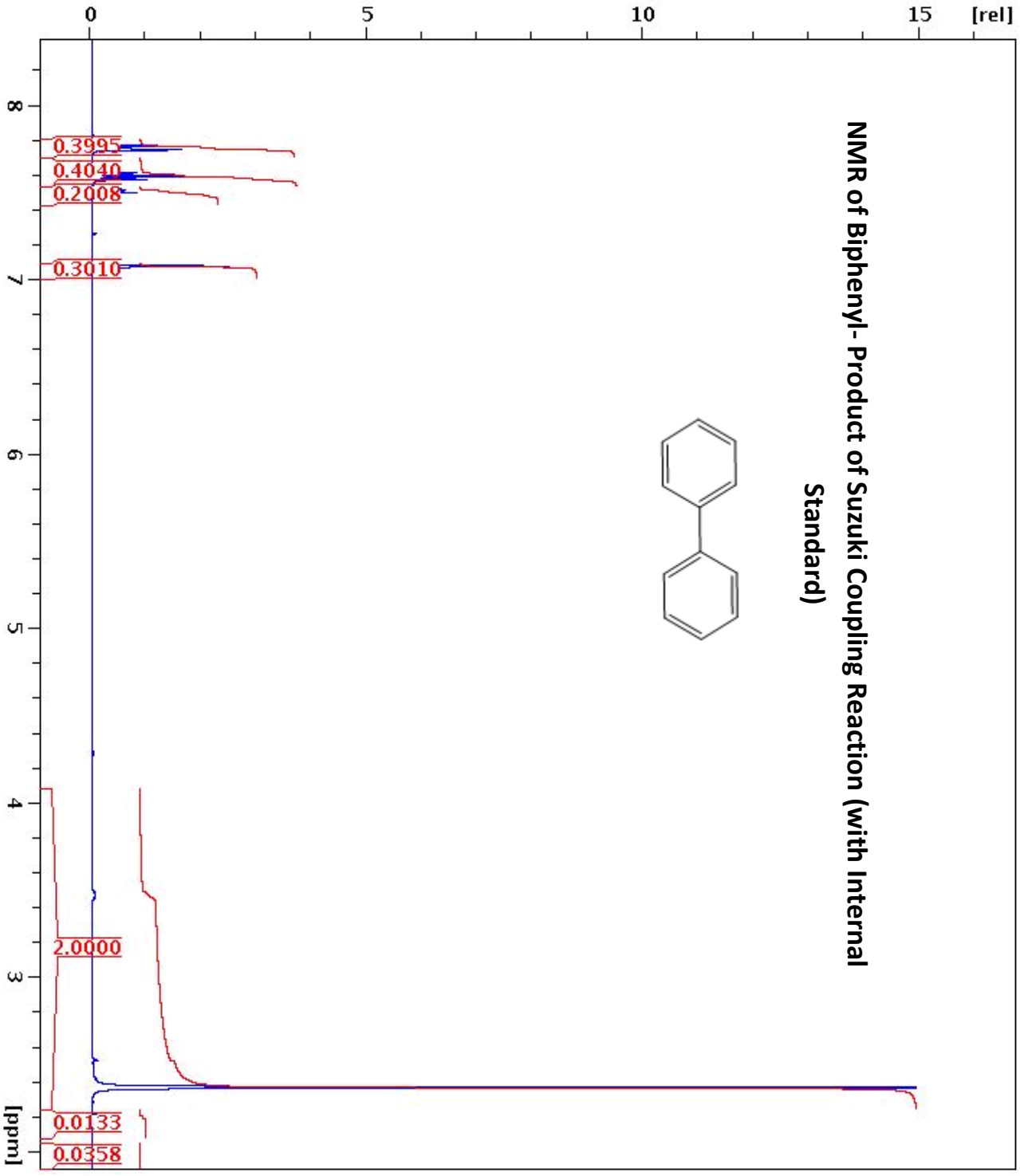

NMR of 1-phenyl-2-(4-phenyl-[1,2,3]triazol-1-yl)-ethanone-
Product of Click Reaction
Top: Microwave Heating,
Bottom: Conventional Heating
[rel]
[ppm]
0
2
4
6
8
10
12
O
N
N
N

A.3b: Suzuki Coupling (Chapter 3)

Detailed Procedure of the Synthesis of Biphenyl from Bromobenzene and Phenylboronic Acid

Phenylboronic acid (136 mg, 1.1 mmol), bromobenzene (160 mg 1 mmol), sodium carbonate (319 mg, 3 mmol), tetra-butyl ammonium bromide (323 mg, 1 mmol), ICP (0.2 mL, 1001 ppm Palladium in 5.1 wt% HCl)) and water (1.8 mL) were added to a 10 mL capacity glass microwave reaction vessel containing a magnetic stirring bar. The reaction vessel was sealed with a septum and then placed into the microwave cavity. The pressure device was put in to place on top of the reaction vessel and the unit was to heat the reaction mixture with stirring to 150 °C, using an initial microwave power of 150 W and holding at this temperature for 5 minutes. After the reaction was complete and the reaction had cooled to at least 50°C, it was ensured that there is no remaining pressure in the reaction vessel before removing it from the microwave cavity. The reaction mixture transferred from the microwave vessel into a separatory funnel to perform an extraction. Ethyl acetate (30 mL) is used to rinse the reaction vessel and is added to the separatory funnel along with water (30 mL). Any solids remaining in the microwave vessel are scraped into the funnel; using a spatula. After stoppering the funnel, the solution is repeatedly shaken and vented. The layers are then allowed to separate. The aqueous layer is removed to an Erlenmeyer flask and the organic layer is washed with saturated sodium chloride solution dried over sodium sulfate. The ethyl acetate is removed on a rotary evaporator leaving a crystalline product to give 1,1'-biphenyl (0.156g; 98% yield). The chemical structure of the

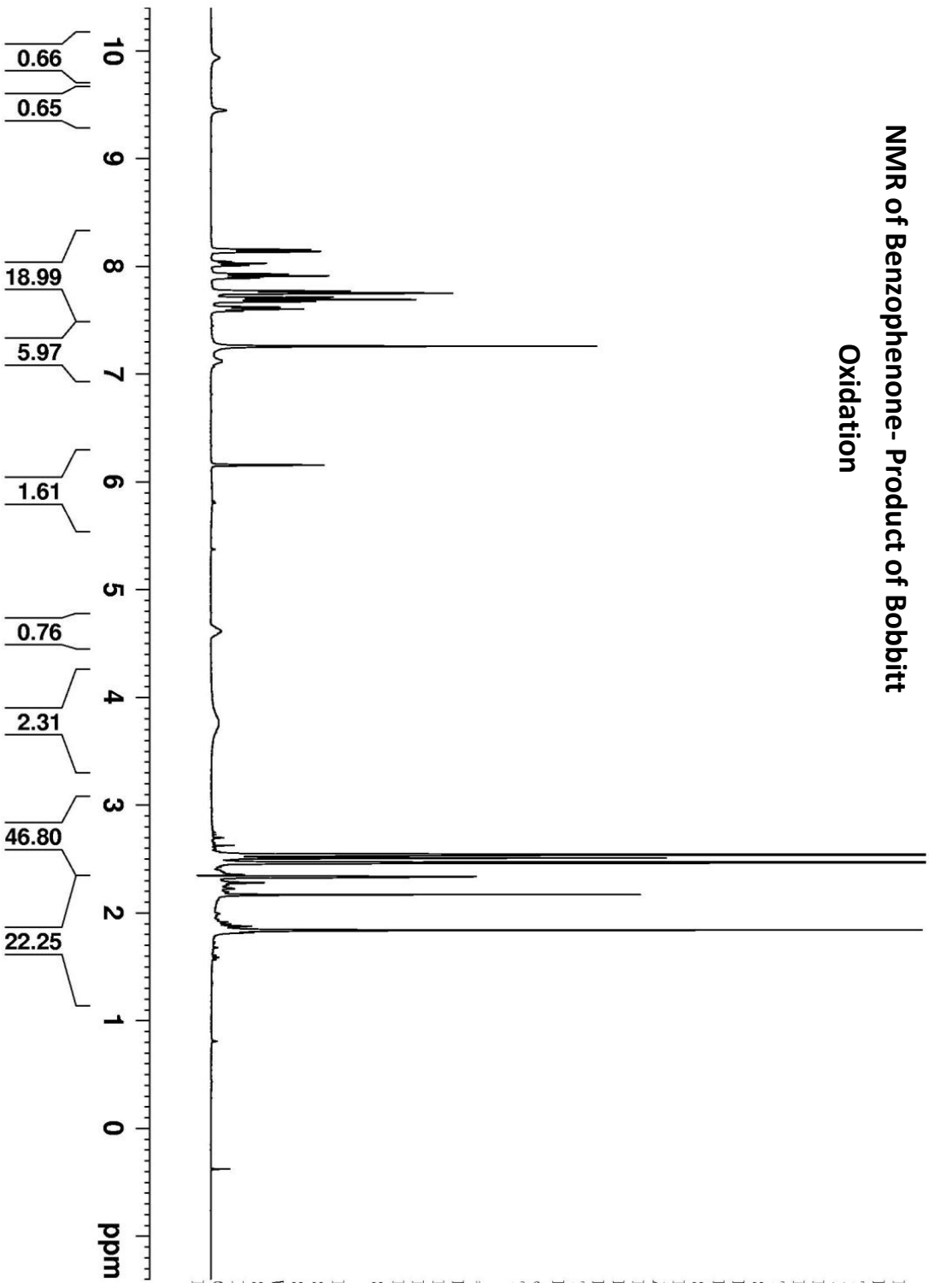
product is confirmed by ^{1}H-NMR spectroscopy using an internal standard, which showed a 66.67% yield.NMR of biphenyl product with internal standard (tetra-methyl benzene: TMB): ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.75 (dd, J= 7.5, 1.5 Hz, 4H), 7.60 (t, J = 7.5 Hz, 4H), 7.45 - 7.49 (m, 2H), 7.08 (s, 2H, TMB), 2.38 (s, 12H, TMB).

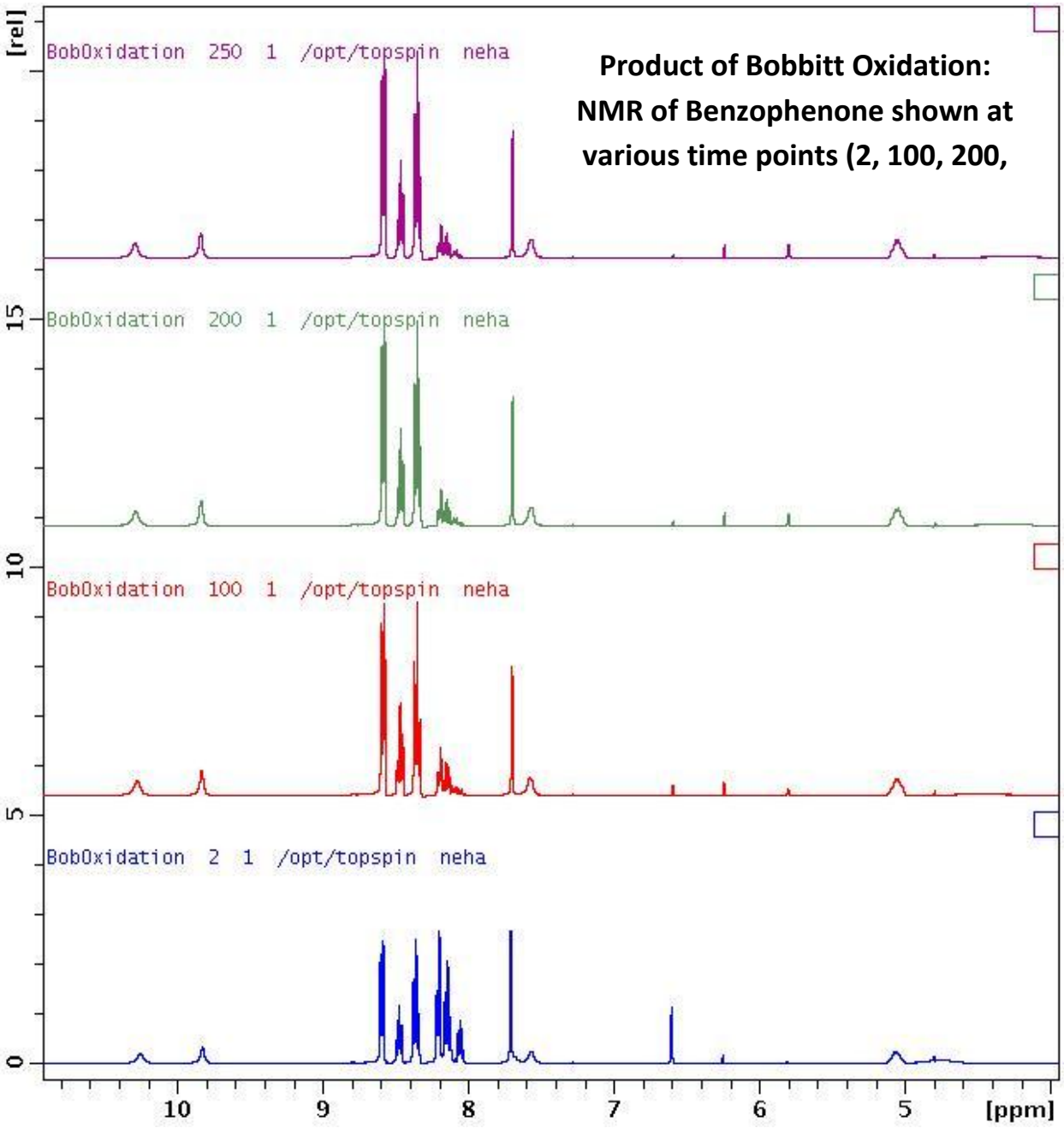


NMR of Biphenyl- Product of Suzuki Coupling Reaction (with Internal Standard)

A.4: In-Situ Reaction Monitoring using Raman Spectroscopy: Bobbitt Oxidation

NMR of Benzophenone- Product of Bobbitt Oxidation
^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 8.15 (dd, J= 7.5, 1.5 Hz, 4H), 8.00 – 8.04 (m, 2H), 7.95 (t, J = 7.5 Hz, 4H).


NMR of Benzophenone- Product of Bobbitt
Oxidation
0.66
0.65
18.99
5.97
1.61
0.76
2.31
46.80
22.25
10
9
8
7
6
5
4
3
2
1
0
ppm



Product of Bobbitt Oxidation: NMR of Benzophenone shown at various time points (2, 100, 200,

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